

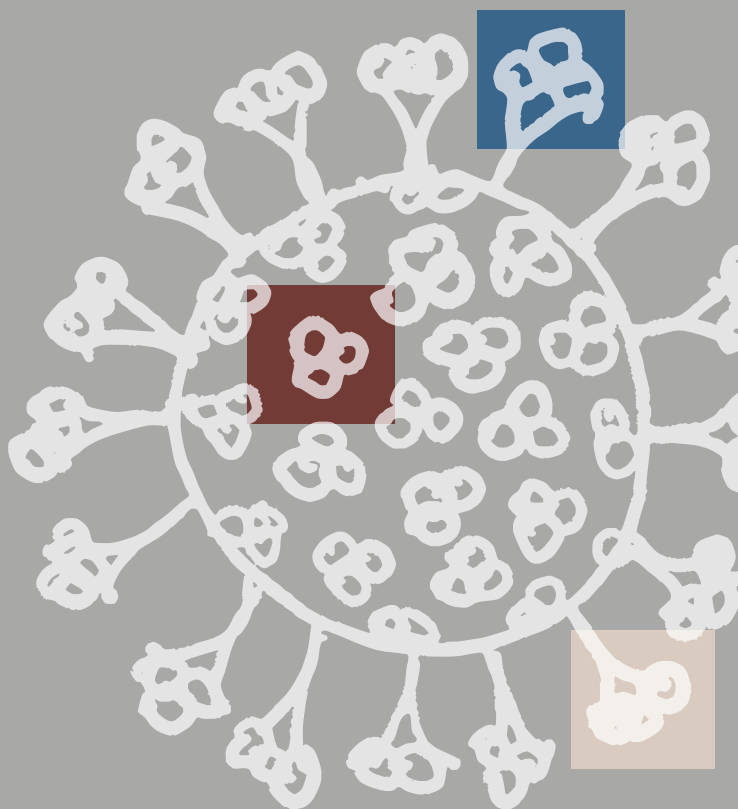


*Bernd Sebastian Kamps
Christian Hoffmann*

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Christian Hoffmann
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Bernd Sebastian Kamps
Christian Hoffmann

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Bernd Sebastian Kamps, M.D.

www.Amedeo.com

Christian Hoffmann, M.D.

Infektionsmedizinisches Centrum

Hamburg MVZ PartG (ICH)

ICH Stadtmitte

Glockengiesserwall 1

20095 Hamburg

researchgate.net/profile/Christian_Hoffmann8

Copy-Editor

[Rob Camp](#)

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PREFACE

Second waves, third waves, never ending waves – as the world is about to enter the second year of the SARS-CoV-2 pandemic, people realize that they are just at the beginning of a global health and economic crisis. In the Northern Hemisphere, the 6 dark autumn and winter months have begun and the world is holding its breath: will the new coronavirus follow the track of the 1918 flu epidemic, relatively mild in spring and devastating in autumn and winter?

There is no doubt that the immense resources of medicine and biotechnology will soon produce a safe and effective vaccine; however, only fools expect mass vaccinations before the middle of 2021 and a measurable impact on the pandemic before 2022.

In the meantime, people around the globe will reduce their contacts with other people and perfect their skills of social distancing. They will continue to wear face masks next year, the year after and maybe beyond. It isn't fun but it must be done.

Bernd Sebastian Kamps & Christian Hoffmann

1 November 2020

PREFACE TO THE FIRST EDITION

Seventeen years ago, in the middle of the outbreak, we decided to write a short medical text about the ongoing SARS drama, presenting the scientific data and providing real-time updates. After publishing three editions in 6 months, a [scientific magazine](#) concluded that our *SARS Reference* (www.SARSReference.com) was “not fancy”, but presented “plenty of information”. When we became aware of the new coronavirus epidemic in mid-January 2020, we immediately felt that time had come to repeat our millennium exercise.

While SARS-CoV-2 seems under control in China, the epidemic is moving west briskly. What only weeks ago seemed an impossible feat – imposing and enforcing strict quarantine measures and isolating millions of people – is now a reality in many countries. People all over the world will have to adapt and invent new lifestyles in what is the most disruptive event since World War II.

We believe that the current situation needs a new type of textbook. Humanity is confronting an unknown and threatening disease which is often severe and fatal. Health care systems are overwhelmed. There is no proven treatment and vaccines will not be available soon. Such a situation has not existed since the flu pandemic in 1918.

We believe a clear head is crucial in times of over-information, with dozens of scientific papers published *every day*, news about hundreds of studies being planned or already on the way and social media blending hard data with rumors and fake news. The tedious work of screening the scientific literature and the scientific data has to be done – regularly & constantly, like a Swiss watch.

Over the coming months, COVID Reference will be presenting updates on a weekly basis and narrating the scientific data as coherently as possible.

Remember [Science Magazine](#). It isn't fancy.

[Bernd Sebastian Kamps](#) & [Christian Hoffmann](#)

29th March 2020

CONTRIBUTING AUTHORS

Thomas Kamradt, M.D.

Professor of Immunology
President, German Society of Immunology
Institute of Immunology
University Hospital Jena
Leutragraben 3
D – 07743 Jena
[linkedin.com/in/thomas-kamradt-93816ba5](https://www.linkedin.com/in/thomas-kamradt-93816ba5)

Stefano Lazzari, M.D.

Specialist in Public Health and Preventive Medicine
International Consultant in Global Health
Former WHO Director
[linkedin.com/in/stefano-lazzari-79a933a](https://www.linkedin.com/in/stefano-lazzari-79a933a)

Jennifer Neubert, M.D.

Department of Pediatric Oncology,
Hematology and Clinical Immunology
Center for Child and Adolescent Health
Medical Faculty
Heinrich-Heine-University Düsseldorf

Tim Niehues, M.D.

Centre for Child and Adolescent Health
Helios Klinikum Krefeld
Lutherplatz 40
D – 47805 Krefeld
https://www.researchgate.net/profile/Tim_Niehues

Wolfgang Preiser, M.D.

University of Stellenbosch
Division of Medical Virology
Tygerberg Campus
PO Box 19063, Tygerberg 7505, South Africa

Matthias Richl, M.D., MBA

Consultant

InnKlinikum Mühldorf

Department of Anaesthesiology and Intensive Care Medicine

Krankenhausstraße 1

84453 Mühldorf am Inn

Peter Rupp M.D., MHA

Consultant and Head of Department

InnKlinikum Mühldorf

Department of Emergency Medicine

Krankenhausstraße 1

84453 Mühldorf am Inn

Markus Unnewehr, M.D

Consultant and Head of Department

St. Barbara-Klinik Hamm

Department of Respiratory Medicine and Infectious Diseases

Am Heessener Wald 1

59073 Hamm

<http://linkedin.com/in/markus-unnewehr-36a3161b9>

Emilia Wilson, M.D.

University of Stellenbosch

Division of Medical Virology

Tygerberg Campus

PO Box 19063, Tygerberg 7505, South Africa

COVID REFERENCE INTERNATIONAL

All collaborators are volunteers

Español

Anisha Gualani Gualani

Medical student, Universidad de Sevilla-US

Jesús García-Rosales Delgado

Medical student, Universidad de Sevilla-US

Italiano

Alberto Desogus

Emeritus oncologist, Oncological Hospital, Cagliari

Stefano Lazzari

M.D., Specialist in Public Health and Preventive Medicine

International Consultant in Global Health

Former WHO Director

Grazia Kiesner (Italian)

Medical Student, Università degli Studi di Firenze

Português

Joana Catarina Ferreira Da Silva

Medical student, University of Lisbon

Sara Mateus Mahomed

Medical student, University of Lisbon

Français

Bruno Giroux

M. D., Paris

Georges Mion

Professor, M.D., Service d'anesthésie réanimation, Hôpital Cochin Paris

Türkçe

Zekeriya Temircan

Ph.D. in Health/Clinic Psychology

Neuropsychology Department

Turkey

Fusun Ferda Erdoğan

Professor, Erciyes University Neurology Department/

Pediatric Neurology

Gevher Nesibe Genom and Stem Cell Institute Neuroscience Department

Turkey

Dilara Güngör

Istanbul University/Çapa Medical School Student

Turkey

Türev Demirtas

M.D., Erciyes University Faculty of Medicine

History of Medicine and Ethics Department

Kayseri / Turkey.

Tiếng Việt

Khanh Phan Nguyen Quoc

M.D., Oxford University Clinical Research Unit

Nam Ha Xuan

Medical student, Hue University of Medicine and Pharmacy

Kim Le Thi Anh (Vietnamese)

Medical student, School of Medicine and Pharmacy, Vietnam National University

Hanoi

Deutsch

Ulf Lüdeke

www.Sardinienintim.com

Copy-Editor

Rob Camp

Art

Attilio Baghino

Cover

Félix Prudhomme

YouTube: [IYENSS](#)

Thomas Splettstösser

SciStyle (Figures)

IT Support

Stephan K.

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0. Top 10

Please bookmark www.CovidReference.com/Top10 and come back every day for the **Daily Top 10 Papers** on COVID-19. Each citation comes with a short comment and a link to the full-text article.

1. Epidemiology

Bernd Sebastian Kamps

Stefano Lazzari

In December 2019, several patients from Wuhan, People's Republic of China, developed pneumonia and respiratory failure reminiscent of the SARS epidemic in 2003 (WMHC 2019, www.SARSReference.com). In early January 2020, a new virus, later denominated SARS-CoV-2, was isolated from bronchoalveolar lavage fluid samples and found to be a betacoronavirus (Zhou 2020). The virus spread first within China (Yu X 2020) and to several countries in Asia before reaching Iran and Italy where it caused major outbreaks. During the first 11 weeks of the pandemic, almost two-thirds of first cases in affected countries were in people reported to have recently travelled from only three affected countries (China, Iran, or Italy), showing how international travel from a few countries with substantial SARS-CoV-2 transmission might have seeded additional outbreaks around the world (Dawood 2020).

Despite some early successes in containment, SARS-CoV-2 eventually took hold in both Europe and North America during the first two months of 2020: in Italy around the end of January, in Washington State around the beginning of February, followed by New York City later that month (Worobey 2020 - see also Figure 6, Deng X 2020, McNeil Jr DG). In Brazil, it was found that there had been more than 100 international virus introductions, with 76% of Brazilian strains falling into three clades that were introduced from Europe between 22 February and 11 March 2020 (Candido 2020).

Between then and the time of this writing (31 October), SARS-CoV-2 has spread to every corner of the world. More than 40 million people have been diagnosed with SARS-CoV-2 infection and more than a million people have died of COVID-19, the disease caused by SARS-CoV-2. Not all cases, in particular if asymptomatic, have been diagnosed and the true number of infections and deaths is probably much higher. Relatively few large scale seroprevalence studies have been completed but the available seroprevalence data show that only a few places, like Mumbai and Manaus, have reached a high prevalence in the population, close to the level required for some kind of herd immunity (see Table 1). [Herd immunity is defined as the proportion of a population that must be immune to an infectious disease, either by natural infection or vaccination, to provide indirect protection (herd protection) to those who are not immune to the disease (D'Souza 2020, Adam 2020).

Table 1 shows that countries hit hardest by the COVID-19 pandemic have higher seroprevalence rates but, without an effective vaccine, no country can count on any kind of herd immunity in the near future.

Table 1. Seroprevalence data 2020

		Sample collection		
Italy*	Nationwide	May 25-July 15	2.5%	Sabbadini 2020
Italy	Lodi (red zone)		23%	Percivalle 2020
Spain	Nationwide		5.0%	Pollán 2020
	Madrid		>10%	
Spain	Madrid		11%	Soriano 2020
Switzerland	Geneva		5.0- 11%	Stringhini 2020
Denmark	Faroe Islands		0.6%	Petersen 2020
UK	UK		6%	Ward 2020
	London		13%	
	South West		3%	
China	Wuhan	March 9-April 10	3.2- 3.8%	Xu X 2020
US	New York City	March 23-April 1	6.9%	Havers 2020
	San Francisco Bay area	April 23-27	1.0%	
US	New York State		14%	Rosenberg 2020
US	NYC, Health care personnel		13.7%	Moscola 2020
US	Nationwide in patients receiving dialysis	July 2020	8.3%	Anand 2020
India	Mumbai	July	57%	Kolthur-Seetharam 2020
Brazil	Manaus	March-August	66%	Buss 2020 Not peer-reviewed. Results have recently been questioned.

* Note that Italy's national survey results are preliminary and probably an underestimation. The country only managed to collect 40% of the planned samples, with many people refusing to be tested. Insiders never believed these figures and favored a seropositivity rate of 5-10% like in Spain or in France. Now we have a new estimate of COVID-19 prevalence in Italy by Francesca Bassi and colleagues: 9%, corresponding to almost 6 million Italians (Bassi 2020).

The articles cited in Table 1 report some interesting findings:

- **Wuhan** – Seropositivity for IgM and IgG antibodies was low (3.2%–3.8%) even in a highly affected city like Wuhan (Xu X 2020).
- **New York City** – In New York, the prevalence of SARS-CoV-2 among health care personnel was 13.7% (5523 of 40,329 individuals tested) (Moscola 2020) which was similar to that among adults randomly tested in New York State (14.0%) (Rosenberg 2020).
- **UK** – Black, Asian and minority ethnic (BAME) individuals were between two and three times as likely to have had SARS-CoV-2 infection compared to white people. An interesting trend: young people aged 18–24 had the highest rates (8%), while older adults aged 65 to 74 were least likely to have been infected (3%).
- **Mumbai** – In a cross-sectional survey the prevalence of past SARS-CoV-2 infection in three areas in Mumbai was around 57% in the slum areas of Chembur, Matunga and Dahisar, and 16% in neighboring non-slums (Kolthur-Seetharam 2020). In some places of the world herd immunity may be within reach.
- **Geneva** – Young children (5–9 years) and older people (≥ 65 years) had significantly lower seroprevalence rates than other age groups (Stringhini 2020).
- **Faroe Islands** – At the beginning of the pandemic, small islands tended to have low seropositivity rates.

It is worth noting that we still have few nationwide population-based seroprevalence studies, that the sensitivity and specificity of serological tests being used can vary from place to place, and that some people might have been infected without showing detectable levels of antibodies. Based on all available serological studies, WHO has estimated that around 10% of the world population, or 760 million people, might have been infected as of October 2020. <https://www.euronews.com/2020/10/05/around-10-of-the-world-s-population-may-have-had-covid-19-according-to-who>

The mean incubation period of SARS-CoV-2 infection is around 5 days (Li 2020, Lauer 2020, Nie X 2020). The serial interval – defined as the duration of time between a primary case-patient having symptom onset and a secondary case-patient having symptom onset – has been estimated to be between 5 and 7.5 days (Cereda 2020). SARS-CoV-2 is highly contagious, with an estimated basic reproduction number R_0 of around 2.5–3.0 (Chan 2020, Tang B 2020, Zhao 2020). [R_0 indicates the average number of infections one case can generate over the course of the infectious period in a naïve, uninfected population.

Read the guide by David Adam ([Adam 2020](#)) for more precious information on R_0 .]

Prevention

SARS-CoV-2 is easily transmissible both by symptomatic and asymptomatic individuals, thrives in closed and densely inhabited environments, and is amplified by so-called ‘superspreader’ events.

The five golden rules to minimize the risk of SARS-CoV-2 infection

1. Wear face masks in public spaces.
2. Keep a distance of 2 (two!) meters to other people.
3. Avoid **crowded** places (more than 5-10 people).
4. Avoid in particular **crowded** and **closed** spaces (even worse: air-conditioned closed places where air is being moved around).
5. Avoid in all circumstances - **crowded**, **closed** and **noisy** spaces where people must shout to communicate. These are SARS-CoV-2’s preferred playgrounds.

Find below a detailed discussion of SARS-CoV-2 transmission (pages 91) and its prevention (page 145).

As with the earlier SARS and MERS outbreaks ([Shen Z 2004](#), [Cho SY 2016](#)), the spread of SARS-CoV-2 is characterized by the occurrence of so-called “super-spreaders events” where one source of infections seems responsible for a large number of secondary infections. ([Wang L 2020](#)) This phenomenon is well described by a recent study of SARS-CoV-2 transmission in Hong-Kong ([Adam DC 2020](#)). The authors analyzed all clusters of infection in 1038 cases that occurred between January and April 2020 and concluded that 19% of cases were responsible for causing 80% of the additional community cases, with large clusters originating from bars, weddings, and religious ceremonies. Interestingly, decreased delays in confirmation of symptomatic cases did not influence the rate of transmission (suggesting higher rate of transmission at or before symptom onset), whereas rapid contact tracing and quarantine of contacts was very effective in terminating the transmission chain. Other authors ([Endo 2020](#)) have estimated a k of 0.1 outside China, meaning that only 10% of infected individuals transmit the virus (k or *dispersion factor* describes, in mathematical models, how much the disease tends to cluster).

A relatively low dispersion factor with few infected people causing most transmissions could explain some puzzling aspects of the beginning of the COVID-19 pandemic. For example, why the early introductions in Europe of SARS-CoV-2 in December 2019 ([France](#)) and in January 2020 ([France](#), [Germany](#)) did not result in earlier outbreaks. Or why the large outbreak in Northern Italy in February 2020 did not lead to a similar rapid spread of the virus in the rest of the country.

Understanding the reasons underlining superspreader events can be key to the success of preventive measures, so the big question is, “Why do some COVID-19 patients infect many others, whereas most don’t spread the virus at all?” ([Kupferschmidt 2020](#)). It is possible that some individuals simply shed more virus than others, or that there is much more shedding at a specific moment of higher contagiousness in the natural history of the infection, possibly when viral load is at its peak. Environmental conditions also clearly play a role, with crowded, closed places where people talk loudly, shout, sing or exercise being at higher risk, possibly because of the higher production and diffusion of small particles like aerosols. A “superspreader individual” in a “superspreading setting” may result in a very large number of infections, as seen in the Shincheonji church cluster in [South Korea where, in March 2020, one single person was estimated to have generated more than 6000 cases](#).

A better understanding of superspreader events may help in defining the most effective measures to reduce SARS-CoV-2 transmission by reducing the likelihood of superspreading events. We will explore below the most common “hotspots” of SARS-CoV-2 infection, where the likelihood of single or multiple infections is higher.

In this chapter, we will discuss:

1. Hotspots of SARS-CoV-2 infection
2. Special aspects of the pandemic in selected places
3. The Pandemic: Past and Future

Hotspots of SARS-CoV-2 Transmission

The following settings were, are or can be catalyzers of outbreaks:

- Hospitals
- Nursing facilities
- Homes (also including intense social life with friends and colleagues)

- Leisure facilities such as bars, clubs, choirs, discos, sports facilities and restaurants
- Workplaces
- Schools
- Mass gatherings
 - Marriages
 - Funerals
 - Religious gatherings
- Closed and densely populated spaces
 - Prisons
 - Homeless shelters
 - Ships (closed spaces)
 - Cruise ships
 - Aircraft carriers and other military vessels

Hospitals

During the first months of the SARS-CoV-2 pandemic, when suspicion of the disease was low, transmission in hospitals and other health care centers (including doctors offices) played a prominent role in the origin and spread of local epidemics. This was reminiscent of SARS and of the largest MERS outbreak outside of the Arabian peninsula which occurred in the Republic of Korea in 2015, where 184 of 186 cases were infected nosocomially ([Korea Centers for Disease Control and Prevention 2015](#)). Hospitals, as many other places where strangers meet, can be a favorable environment for the propagation of SARS-CoV-2 ([Wison 2020](#)). Within the first 6 weeks of the epidemic in China, 1716 cases and at least 5 deaths (0.3%) were confirmed among health care workers by nucleic acid testing ([Wu 2020](#)). In some instances, hospitals could have been even the main COVID-19 hub, facilitating transmission between health workers and uninfected patients ([Nacoti 2020](#)).

One hospital environment study reports that the virus was widely present in the air and on object surfaces in both the intensive care units and general wards, implying a potentially high infection risk for medical staff. Contamination was greater in ICUs ([Self 2020](#)). Virus RNA has been found on floors, computer mice, trash cans, sickbed handrails, and was detected in the air up to approximately 4 m from patients ([Guo 2020](#)). The virus was also isolated from toilet bowl and sink samples, suggesting that viral shedding in stool could be a potential route of transmission ([Young 2020](#), [Tang 2020](#)). However,

most of these studies have evaluated only the presence of viral RNA, not its infectivity.

Although nosocomial spread of the virus is well documented, appropriate hospital infection control measures can prevent nosocomial transmission of SARS-CoV-2 ([Chen 2020](#), [Nagano 2020](#), [Callaghan 2020](#)). This was nicely demonstrated by the case of a person in her 60s who travelled to Wuhan on Dec 25, 2019, returned to the US on Jan 13, 2020, and transmitted SARS-CoV-2 to her husband. Although both were hospitalized in the same facility and shared hundreds ($n = 348$) of contacts with HCWs, nobody else became infected ([Ghinai 2020](#)).

However, working in a high-risk department, longer duty hours, and sub-optimal hand hygiene after coming into contact with patients are all associated with an increased risk of infection in health care workers ([Ran 2020](#)). At one time, during the early epidemic in March 2020, around half of 200 cases in Sardinia were among hospital staff and other health care workers. On 14 April, the US CDC reported that [9282 Health Care Personnel](#) had been infected with SARS-CoV-2 in the US. Health care workers from COVID-19 have a higher risk of being SARS-CoV-2 infected (5.4%) than those from non-COVID units (0.6%) ([Vahidy 2020](#)). In a prospective cohort study in London, 25% of HCWs were already seropositive at enrolment (26 March to 8 April) and a further 20% became seropositive within the first month of follow-up ([Houlihan 2020](#)). However, a Chinese study of 9684 healthcare workers (HCW) in Tongji Hospital showed a higher rate of infection in non-first-line HCW (93/6,574, 1.4%) when compared to those who worked in fever clinics or wards (17/3110, 0.5%) ([Lai X 2020](#)). Interpretation: those who worked in clinical departments other than fever clinics and wards may have had less access to, or have neglected to adopt, adequate protective measures.

The risk factors for SARS-CoV-2 infection in health care workers have been summarized in a recent review ([Chou 2020](#)). There is evidence that more consistent and full use of recommended PPE measures was associated with decreased risk for infection. Association was most consistent for masks but was also observed for gloves, gowns, and eye protection, as well as hand hygiene. Some evidence was found that N95 respirators might be associated with higher reduction of risk for infection than surgical masks. Evidence also indicated an association with certain exposures (such as involvement in intubations, direct contact with infected patients, or contact with bodily fluids).

SARS-CoV-2 outbreaks have also been documented in dialysis units ([Schwierzeck 2020](#), [Rincón 2020](#)). The prevalence of SARS-CoV-2 antibodies was lower among personnel who reported always wearing a face covering

while caring for patients (6%), compared with those who did not (9%) (Self 2020).

Long-term care facilities

Long-term care facilities (LTC) are high-risk settings for infectious respiratory diseases. The first important study published in May 2020 reported an outbreak in a skilled nursing facility in King County, Washington, US, where 167 cases of COVID-19 (101 residents, 50 health care personnel and 16 visitors) were diagnosed within less than three weeks from the identification of the first case: (McMichael 2020) (Table 2).

Table 2. COVID outbreak in a long-term care facility

	Residents (N = 101)	Healthcare personnel (N = 50)	Visitors (N = 16)
Median age (range)	83 (51-100)	43.5 (21-79)	62.5 (52-88)
Female (%)	68.3	76	31.2
Hospitalized (%)	54.5	6.0	50.0
Died (%)	33.7	0	6.2
Chronic underlying conditions (%)			
Hypertension	67.3	8.0	12.5
Cardiac disease	60.4	8.0	18.8
Renal disease	40.6	0	12.5
Diabetes mellitus	31.7	10.0	6.2
Obesity	30.7	6.0	18.8
Pulmonary disease	31.7	4.0	12.5

Among residents (median age: 83 years), the case fatality rate was 33.7%. Chronic underling conditions included hypertension, cardiac disease, renal disease, diabetes mellitus, obesity, and pulmonary disease. The study demonstrated that once introduced in a long-term care facility, often by a care worker or a visitor, SARS-CoV-2 has the potential to spread rapidly and widely, with devastating consequences.

By mid-April 2020, more than 1300 LTC facilities in the US had identified infected patients (Cenziper 2020, CDC 200311). As most residents had one or more chronic underling conditions such as hypertension, cardiac disease, renal disease, diabetes mellitus, obesity and pulmonary disease, COVID-19 put them at very high risk for premature death.

Later studies found a high percentage of asymptomatic residents (43%) during the two weeks prior to testing (Graham 2020b); extraordinarily high sero-

positivity rates (72%; [Graham 2020a](#)); and a higher infection rate in residents (9.0%) than in staff (4.7%) ([Marossy 2020](#)).

A national survey covering 96% of all long-term care facilities in Italy found that in Lombardy, the epicenter of the epidemic, 53.4% of the 3045 residents who died between 1 February and 14 April were either diagnosed with COVID-19 or presented flu-like symptoms. Among the 661 residents who were hospitalized during the same period, **199 (30%) were found positive by a PCR test.**

As soon as a single case is detected among residents of a nursing facility, it is recommended to test all residents, as many of them may still be asymptomatic. After an outbreak at a long-term care nursing facility, all residents, regardless of symptoms, underwent serial (approximately weekly) nasopharyngeal SARS-CoV-2 RT-PCR testing. Nineteen of 99 (19%) residents had positive test results for SARS-CoV-2 ([Dora 2020](#)). Fourteen of the 19 residents with COVID-19 were asymptomatic at the time of testing. Among these, eight developed symptoms 1-5 days after specimen collection and were later classified as pre-symptomatic.

Mortality in LTCs is almost always high. In a study from Ontario, Canada, the incidence of mortality was more than 13 times higher than the one seen in community-living adults older than 69 years during a similar period ([Fisman 2020](#)). In one UK investigation involving 394 residents and 70 staff in 4 nursing homes in central London, 26% of residents died over a two-month period ([Graham 2020](#)). It is estimated that residents in long-term care facilities contributed 30–60% of all COVID-19 deaths in many European countries ([ECDC 2020](#); see also the statement to the press by [Hans Henri P. Kluge, WHO Regional Director for Europe](#)). Excess mortality data suggests that in several countries many deaths in long-term care facilities might have occurred in patients not tested for COVID-19, which are often not included in the official national COVID-19 mortality statistics.

Homes

Infection rates at home varied widely (between 11% and 19%) in three studies. One group noted that household contacts and those travelling with a COVID-19 case had a 6 to 7 times higher risk of infection than other close contacts, and that children were as likely to be infected as adults ([Bi Q 2020](#)). Another group found that the odds of infection among children and young people (< 20 years old) was only 0.26 times that among the elderly (≥ 60 years old) ([Jing QL 2020](#)). A third group calculated that the secondary attack rate in children was 4% compared to 17.1% in adults, and that the secondary attack rate in contacts who were spouses of index cases was 27.8% compared to 17.3% in other adult members in the households ([Li W 2020](#)). It has been objected that

these transmission rates may be an underestimate if index cases were isolated outside of the home (Sun 2020). In yet another study, 32.4% (48 of 148) of household contacts of 35 index cases were infected (Wu J 2020).

In Spain, during the summer of 2020, social settings such as family gatherings or private parties accounted for 14% of cases (854/6208) in an analysis of 551 outbreaks. SARS-CoV-2 positive cases linked to leisure venues such as bars, restaurants, or clubs were even more frequent (NCOMG 2020) (see next paragraph).

Leisure venues (bars, clubs, choirs, karaoke, discos, etc.)

In Spain, an analysis of 551 outbreaks from mid-June to 2 August linked 1230 of 6208 cases (20%) to leisure venues such as bars, restaurants, or clubs (NCOMG 2020). Data from Japan showed that of a total of 61 COVID-19 clusters, 10 (16%) were in restaurants or bars; 7 (11%) in music-related events, such as live music concerts, chorus group rehearsals, and karaoke parties; 5 (8%) in gymnasiums; 2 (3%) in ceremonial functions (Furuse 2020). In South Korea, superspreading events in nightclubs in downtown Seoul were shown to have the potential to spark a local resurgence of cases (Kang 2020). In Hong Kong, an explosive summer outbreak was best explained by the sudden increase in social gatherings after the easing of public health control measures, especially gatherings at eateries (To 2020). College trips and summer camps represent another environment for efficient SARS-CoV-2 transmission. In one case, a spring break trip from Austin to Mexico resulted in 14 asymptomatic and 50 symptomatic cases (Lewis 2020). CDC reported an outbreak with 260 (44%) out of 597 attendees of an overnight summer camp in Georgia becoming infected in June 2020 (Szablewski 2020). The camp adopted most of CDC's suggested preventive measures for Youth and Summer Camps but wearing cloth masks and opening windows and doors for increased ventilation in buildings were not implemented ☹.

Choirs, too, are places of efficient SARS-CoV-2 transmission. On 8 March 2020, the Amsterdam Mixed Choir gave a performance of Bach's St John Passion in the city's Concertgebouw Auditorium. Days later, the first singers developed symptoms and in the end 102 of 130 choristers were confirmed to have COVID-19. One 78-year-old choir member died, as did three partners of choir members; some singers required intensive care (The Guardian, 17 May). On 9 March, members of the Berlin Cathedral Choir met for their weekly rehearsal. Three weeks later, 32 out of 74 choir members were positive for SARS-CoV-2 (NDR 2020). All recovered. On 10 March 2020, 61 members of a Skagit County choir in Washington met for a 2,5-hour practice. A few weeks later, researchers reported that 32 confirmed and 20 probable secondary COVID-19 cases

had occurred (attack rate = 53.3% to 86.7%); three patients were hospitalized, and two died. The authors conclude that transmission was likely facilitated by close proximity (within 6 feet) during practice and increased viral diffusion by the act of singing (Hamner 2020).

In an unintentional experiment, the German national team of amateur boxers proved that even 100% transmission rates can be achieved within days. In a training camp, some of the 18 athletes and 7 coaches and supervisors started having cold symptoms. Four days later, all 25 persons tested positive for SARS-CoV-2 (Anonymous 2020).

These data suggest that any noisy, closed and stagnant air environments (e.g., discos, pubs, birthday parties, restaurants, meat processing facilities, etc.) where people stand, sit or lie close together are ideal conditions for generating large SARS-CoV-2 outbreaks. If they need to shout for communication, the situation may become explosive.

Workplaces

As early as January 2020, SARS-CoV-2 was found to spread during workshops and company meetings (Böhmer 2020). A few weeks later, an outbreak of SARS-CoV-2 infection was reported from a call center where 94 out of 216 employees working on the same floor were infected, translating to an attack rate of 43.5% (Park SY 2020). Particularly instructive is the case of a scientific advisory board meeting held in Munich, Germany, at the end of February. Eight dermatologists and 6 scientists (among them the index patient) met in a conference room of about 70 m² with a U-shaped set-up of tables separated by a central aisle > 1 meter wide. During the meeting that lasted 9,5 hours, refreshments were served in the room 4 times. In the evening, the participants had dinner in a nearby restaurant and shook hands for farewell, with a few short hugs (no kisses!). Finally, the index patient shared a taxi with three colleagues for about 45 min. Outcome: the index patient infected at least 11 of the 13 other participants. When isolated either in a hospital or at home these individuals infected an additional 14 persons (Hijnen 2020). In the presence of an infected individual, workplaces can be important amplifiers of local transmission.

In May 2020, outbreaks with hundreds of infected individuals were reported from meat-packing plants in Germany (DER SPIEGEL), the US (The Guardian) and France (Le Monde). Outbreaks in meat processing facilities were also reported from other countries. In March and April, 25.6% (929) of employees and 8.7% (210) of their contacts were diagnosed with COVID-19 in South Dakota, USA; two employees died (Steinberg 2020). The highest attack rates occurred among employees who worked < 6 feet (2 meters) from one another at

the production line. Another study reported 16,233 COVID-19 cases and 86 COVID-19-related deaths among workers in 239 facilities (Waltenburg 2020). The percentage of workers with COVID-19 ranged from 3.1% to over 20% per facility (Waltenburg 2020). Promiscuity, noise, cold and humid conditions are currently favored as explanations for these unusual outbreaks. In Spain, the above-mentioned analysis of 551 outbreaks from mid-June to 2 August linked around 500 of 6208 cases (8%) to occupational settings, in particular, workers in the fruit and vegetable sector and workers at slaughterhouses or meat processing plants (360/6208 cases) (NCOMG 2020).

Schools

Schoolchildren usually play a major role in the spread of respiratory viruses, including influenza. However, while the SARS-CoV-2 virus has been detected in many children, they generally experience milder symptoms than adults, need intensive care less frequently and have a low death rate. An analysis of data from Canada, China, Italy, Japan, Singapore and South Korea found that susceptibility to infection in individuals under 20 years of age was approximately half that of adults aged over 20 years, and that clinical symptoms are manifest in 21% of infections in 10-to-19-year-olds, rising to 69% of infections in people aged over 70 years (Davis 2020).

The role of children in SARS-COV-2 transmission is still unclear. Several studies have suggested that children rarely transmit the infection. In a small COVID-19 cluster detected in the French Alps at the end of January, one person returning from China infected eleven other people, including a nine-year-old schoolboy. The researchers closely tracked and tested all contacts (Danis 2020). The boy had gone to school after showing COVID-19 symptoms and was estimated to have had more than sixty high-risk close contacts. No one was found positive to the coronavirus, though many had other respiratory infections. Also, no virus was found in the boy's two siblings who were on the same Alpine vacation.

A study by the Institut Pasteur in April 2020 (before school closure) that included 510 primary school children concluded that "it appears that the children did not spread the infection to other students or to teachers or other staff at the schools". Another study in 40 patients less than 16 years old in Geneva, Switzerland (Posfay-Barbe 2020) also concluded that unlike with other viral respiratory infections, children do not seem to be a major vector of SARS-CoV-2 transmission, with most pediatric cases described inside familial clusters and no documentation of child-to-child or child-to-adult transmission."

However, a review of 14 published studies ([Rajmil 2020](#)) was less categorical, simply concluding that children are not transmitters to a greater extent than adults. A more recent metanalysis of published evidence ([Viner 2020](#)) states that there is insufficient evidence to conclude whether transmission of SARS-CoV-2 by children is lower than by adults.

CDC reported in September on twelve children who acquired COVID-19 in three different child-care facilities in Utah. It documented transmission from these children to at least 12 (26%) of 46 non-facility contacts and that transmission was observed from two of three children with confirmed, asymptomatic COVID-19. In addition, several studies have found that both symptomatic and asymptomatic children can shed the SARS-CoV-2 virus for several days or weeks after infection ([Liu 2020](#), [Han 2020](#)). However, qualitative positive or negative findings for molecular detection of virus may not necessarily correlate with infectivity ([DeBiasi 2020](#)).

In the early autumn of 2020, how to re-open schools was a hot debate. In Taiwan authorities established general guidelines, including a combination of strategies such as active campus-based screening and access control; school-based screening and quarantine protocols; student and faculty quarantine when warranted; mobilization of administrative and health center staff; regulation of dormitories and cafeterias; and reinforcement of personal hygiene, environmental sanitation, and indoor air ventilation practices ([Cheng SY 2020](#)). Most European countries have decided to reopen schools, considering the possible increase in infections as being less damaging than the loss of education in schoolchildren. At the time of this writing (31 October), the reopening of schools in European countries does not seem to have contributed substantially to the national epidemics. It can indeed be difficult to determine if children were infected at home, at school (by their peers or by their teachers) or outside during social or sport gatherings. In some school clusters, the index cases identified were teachers and/or parents ([Torres 2020](#)), so school prevention should focus on enforcing preventive measures and avoiding new cases among teachers. In any case, close monitoring of school clusters will provide much needed additional data that might help clarify the role of children of different ages in the spread of the virus, and whether schools can be considered hotspots or not of SARS-CoV-2 transmission.

Mass gatherings

Sports events

A football match played in Milan, Italy on 19 February 2020 has been described as “Game zero” or “a biological bomb”. The match was attended by 40,000 fans from Bergamo and 2500 from Valencia and was played just two days before the first positive case of COVID-19 was confirmed in Lombardy. Thirty-five percent of Valencia’s team members tested positive for the coronavirus a few weeks later, as did several Valencia fans. By mid-March, there were nearly 7,000 people in Bergamo who had tested positive for the coronavirus with more than 1,000 deaths, making Bergamo the most heavily hit province during the initial COVID-19 outbreak in Italy.

Other sport events have been implicated in the COVID-19 spread, including the match between Liverpool and Atletico Madrid, held at Anfield stadium on 11th March and attended by 3,000 supporters from Madrid, the center of the pandemic in Spain, and the Cheltenham horseracing festival, with races attracting crowds of over 60,000 people (Sassano 2020). Most national and international large sport events, [cancelled or postponed in the first half of 2020](#), have resumed during the summer months, though with closed doors or major limitations in the number of spectators. Large sports events including tens of thousands of spectators might not take place for several years.

Religious gatherings

Several mass gathering religious events have been associated with explosive outbreaks of COVID-19. As mentioned above, in April 2020, a total of 5212 coronavirus cases were related to an outbreak at the Shincheonji Church in South Korea, accounting for about 48.7% of [all infections](#) in the country at that time.

The annual gathering of the [Christian Open Door Church](#) held between 17 and 24 February in [Mulhouse, France](#), was attended by about 2500 people and became the first significant cluster in France. After a parishioner and 18 family members tested positive on 1 March, a flurry of reported cases brought the existence of a cluster to light. According to an investigative report by France Info, more than 1,000 infected members from the rally in Mulhouse contributed to the start of the COVID-19 epidemic in France. Many diagnosed cases and deaths in France as well as Switzerland, Belgium and Germany were linked to this gathering.

Another report described 35 confirmed COVID-19 cases among 92 attendees at church events in Arkansas during March 6–11. The estimated attack rates

ranged from 38% to 78% (James 2020). In Frankfurt, Germany, one of the first post-lockdown clusters started during a religious ceremony held on 10 May. As of 26 May, 112 individuals were confirmed to be infected with SARS-CoV-2 (Frankfurter Rundschau). May we suggest that going to church does not protect you from SARS-CoV-2?

Huge religious mass gatherings should probably be postponed. Gatherings that attract millions of pilgrims from many countries (with pilgrims typically > 50 years old and often suffering from chronic disease such as diabetes or cardiovascular disease [Mubarak 2020]) have clearly the potential to create giga-spreading events, saturating designated wards and ICU capacity within days. Reducing the number of pilgrims and excluding foreign pilgrims is therefore a wise decision (Khan 2020). Events attended by even more people, such as the Sabarimala annual 41-day long Hindu pilgrimage (average attendance: 25 million people) would need even more careful planning (Nayar 2020).

Closed and densely populated spaces

Prisons

According to WHO, people deprived of their liberty, such as people in prisons and other places of detention, are more vulnerable to COVID-19 outbreaks (WHO 200315). People in prison are forced to live in close proximity and thus may act as a source of infection, amplification and spread of infectious diseases within and beyond prisons. The global prison population is estimated at 11 million and prisons are in no way “equipped” to deal with COVID-19 (Burki 2020).

In US prisons, COVID-19 attack rates are high. By June 6, 2020, there had been 42,107 cases and 510 deaths among 1.3 million prisoners (Saloner 2020, Wallace 2020). Among 98 incarcerated and detained persons in Louisiana who were quarantined because of virus exposure, 71 (72%) had SARS-CoV-2 infection identified through serial testing, among them 45% without any symptoms at the time of testing (Njuguna 2020). In July 2020, more than one-third of the inmates and staff (1600 people) in San Quentin Prison tested positive (Maxmen 2020). Six had died. Still in July 2020, the rate of COVID-19 among incarcerated individuals in Massachusetts was nearly 3 times that of the general population and 5 times the US rate (Jiménez 2020).

Homeless shelters

Testing in 1192 residents and 313 staff members in 19 homeless shelters from 4 US cities (see table online), initially triggered by the identification of a COVID-19 cluster, found infection rates of up to 66% (Mosites 2020).

In another report from Boston, Massachusetts, 147/408 (36%) homeless shelter residents were positive. Of note, 88% had no fever or other symptoms at the time of diagnosis (Baggett 2020).

In yet another study of 14 homeless shelters in King County, Washington, researchers divided the number of positive cases by the total number of participant encounters, regardless of symptoms. Among 1434 encounters, 29 (2%) cases of SARS-CoV-2 infection were detected across 5 shelters. Eighty-six percent of persons with positive test results slept in a communal space rather than in a private or shared room (Rogers 2020).

Cruise ships, aircraft carriers etc.

Cruise ships carry many people in confined spaces. On 3 February 2020, 10 cases of COVID-19 were reported on the Diamond Princess cruise ship. Within 24 hours, all sick passengers were isolated and removed from the ship and the rest of the passengers quarantined on board. Over time, more than 700 of the 3,700 passengers and crew tested positive (around 20%). One study suggested that without any intervention 2920 individuals out of the 3700 (79%) would have been infected (Rocklov 2020). The study also showed that an early evacuation of all passengers on 3 February would have been associated with only 76 infected. For cruise ships, SARS-CoV-2 may spell disaster – carrying village-loads of people from one place to another may not be a viable business model for years to come.

Big navy vessels such as aircraft carriers can become floating petri dishes for emerging viral respiratory diseases. Already in 1996, an outbreak of influenza A (H3N2) occurred aboard a navy ship. At least 42% of the crew became ill within few days, although 95% had been appropriately vaccinated (Earhart 2001). Since the beginning of the year, several outbreaks of COVID-19 on military ships have been reported, facilitated by the small enclosed areas of work and the lack of private quarters for the crew. The largest outbreaks have been reported on the USS *Theodore Roosevelt* and the French aircraft carrier *Charles de Gaulle*. During the *Theodore Roosevelt* outbreak in late March, around 600 sailors out of a crew of 4800 were infected with SARS-CoV-2 (see also the March 30 entry of the Timeline); around 20% reported no symptoms and one sailor died. (USNI News). Preventive measures, such as using face-coverings and observing social distancing, reduced risk of infection: among 382 service members, those who reported taking preventive measures had a lower infection rate than did those who did not report taking these measures (e.g., wearing a face-covering, 56% versus 81%; avoiding common areas, 54% versus 68%; and observing social distancing, 55% versus 70%, respectively) (Payne 2020).

On the French aircraft carrier *Charles-de-Gaulle*, a massive epidemic was confirmed on 17 April. Among the 1760 sailors, 1046 (59%) were positive for SARS-CoV-2, 500 (28%) presented symptoms, 24 (1.3%) sailors were hospitalized, 8 required oxygen therapy and one was admitted in intensive care. Smaller clusters have also been reported on 5 other US military vessels, and in one each from France, Taiwan, and Holland. However, given usual security policies and communication restrictions of national armies and navies, it is possible that other unreported cluster of cases and even deaths might have occurred.

Special Aspects of the Pandemic

The COVID-19 pandemic has highlighted a number of specific aspects and lessons learned from different countries that should be kept in mind during the management of future pandemics (by coronaviruses, influenza viruses or by as yet unknown viruses):

- First outbreak (China)
- Surprise or unpreparedness (Italy)
- Unwillingness to prepare (UK, USA, Brazil)
- Partial preparedness (France)
- Preparedness (Germany)
- Herd immunity? (Sweden)
- Deferred beginning (South America)
- Splendid isolation (New Zealand, Australia)
- Unknown (?) outcome (Africa)

First outbreak (China)

China was caught by surprise by the COVID-19 outbreak – as any other nation would have been – but “thanks” to the SARS outbreak in 2003 ([Kamps-Hoffmann 2003](#)), was prepared for it. At first, the epidemic spread within Wuhan and Hubei Province (December 2019, [Li Q 2020](#)) and then nationwide to all provinces in January 2020, favored by travelers departing from Wuhan before the Chinese Spring Festival ([Zhong 2020](#), [Jia JS 2020](#)). However, within 3 weeks from the identification of the new virus, the government ordered the lockdown of more than 50 million people in Wuhan and the surrounding province of Hubei, as well as travel restrictions for hundreds of millions of Chinese citizens. This astonishing first in human history achieved what even

specialists didn't dare dream: curbing an epidemic caused by a highly contagious virus (Lau 2020).

As early as four weeks after the Wuhan lockdown, there was evidence that strict containment measures were capable of curbing a SARS-CoV-2 epidemic as shown in Figure 1 (page 35). The lesson from China: it is possible to lockdown entire provinces or countries and lockdown works. Some authorities in the Western Hemisphere followed the example of China (Italy, for example, ordered a lockdown as early as 18 days after the diagnosis of the first autochthonous case), other governments did not. It cannot be overemphasized that China has basically managed to control the spread of SARS-CoV-2 since March. How was that possible (Burki 2020)?

Preparedness (Taiwan, Vietnam, Japan)

On 7 June, **Taiwan** (24 million people with a population density of 650/km²) had reported only 443 cases and 7 deaths. Most SARS-CoV-2 infections were not autochthonous. As of 6 April 2020, 321 cases were imported by Taiwanese citizens who had travelled once or more to 37 countries for tourism, business, work, or study (Liu JY 2020). From the beginning, Taiwan drew on its SARS experience to focus on protecting health care workers' safety and strengthening pandemic response (Schwartz 2020 + The Guardian, 13 March 2020). An early study suggested that identifying and isolating symptomatic patients alone might not suffice to contain the epidemic and recommended more generalized measures such as social distancing (Cheng HY 2020). Big data analytics were used in containing the epidemic. On one occasion, authorities offered self-monitoring and self-quarantine to 627,386 persons who potentially had contact with the more than 3,000 passengers of a cruise ship. These passengers had disembarked at Keelung Harbor in Taiwan for a 1-day tour five days before the COVID-19 outbreak on the Diamond Princess cruise ship on February 5, 2020 (Chen CM 2020).

Vietnam, too, did remarkably well. One hundred days after the first SARS-CoV-2 case was reported in Vietnam on January 23rd, 270 cases were confirmed, with no deaths. Although there was a high proportion of asymptomatic and imported cases as well as evidence for substantial pre-symptomatic transmission, Vietnam controlled SARS-CoV-2 spread through the early introduction of mass communication, meticulous contact-tracing with strict quarantine, and international travel restrictions (Pham QT 2020).

Finally, in **Japan**, public adherence to the rules, along with cluster tracing and a ban on mass gatherings, seem to have helped in bringing the outbreak

under control. Where widespread mask use and hygiene is a normal part of etiquette, combatting SARS-CoV-2 is easier (Looi 2020).

Experiences from these countries show that effective testing and contact tracing, combined with physical distancing measures, can keep the pandemic at bay and an economy open. Health is the key to wealth.

Surprise or unpreparedness (Italy)

In Italy and France, SARS-CoV-2 was circulating as early as January among asymptomatic or pauci-symptomatic people (Cereda 2020, Gámbaro 2020). Italy was the first European country struck by the pandemic. Complete genome analysis of SARS-CoV-2 isolates suggests that the virus was introduced on multiple occasions (Giovanetti 2020). Although the first local case was diagnosed only on 20 February, the force of the outbreak suggests that the virus had been circulating for weeks, possibly as early as 1 January (Cereda 2020).

However, it was not straightforward to decipher the subtle signs of coming events, in Italy as elsewhere. During the yearly flu season, COVID-19 deaths in elderly people could easily be interpreted as flu deaths. And the rapid spread of SARS-CoV-2 among the most active social age group – young people crowded in bars, restaurants and discos – would not have caused visible life-threatening symptoms. Before being detected, the epidemic had plenty of time (at least a month) to grow.

One additional possible reason for the delay in recognizing the encroaching epidemic in Italy might have been the Italian ‘suspected case definition for COVID-19’. It included (like the suspected [case definitions recommended at that time by WHO](#)) the mandatory epidemiological criteria of ‘history of travel to China or in contact with a person from China’ before requesting a PCR test. A strict application of this case definition discouraged testing suspected pneumonia cases where the link with China was not clear (which would eventually happen everywhere after the first asymptomatic infections). The anesthesiologist who eventually requested the PCR test for Mattia, the Italian patient #1, did it “[under her own responsibility since not in line with MOH guidelines](#)”.

It is as yet unclear why the epidemic took such a dramatic turn in the northern part of Italy, especially in Lombardy (Gedi Visual 2020), while other areas, especially the southern provinces, were relative spared. Overdispersion might be an explanation (see above). Of note, healthcare in Italy is run regionally and for a long time, the Lombardy Region has favored the development of a mostly private and hospital-centered system, with great facilities but poor community-based services. This meant that COVID-19 patients were quickly

run to the hospital, even with minor symptoms, resulting in overcrowded emergency services and major nosocomial spread. A more decentralized and community-based system like in the [Veneto Region](#) (plus maybe a bit of luck) could have greatly reduced the mortality from COVID-19 in Lombardy. In addition, Italy had not updated nor implemented the 2006 national pandemic preparedness plan (<https://www.saluteinternazionale.info/2020/04/cera-una-volta-il-piano-pandemico>). The lack of preparedness and the overlap of responsibilities hampered considerably the initial coordination of the national response between the regions and the central government.

Unwillingness to prepare, or denial (UK, Iran, USA, Brazil)

In the UK, clumsy political maneuvering delayed the start of effective lockdown measures by a week or more. As the epidemic doubles in size about every 7 days ([Li 2020](#)), around 50% and 75% of all deaths might have been prevented had lockdown or social distancing measures been ordered one or two weeks earlier, respectively. Early data from [Ireland and the United Kingdom](#) seem to confirm this assumption. Each day of delay increased mortality risk by 5 to 6% ([Yehya 2020](#)). The consequences were dramatic ([Stoke 2020](#), [Maxmen 2020](#)).

Like in Iran, where the regime covered up news of the coronavirus for three days to avoid impacting on the turnout at parliamentary elections on 21 February, domestic politics (or paranoia; [BMJ](#), 6 March 2020) influenced the epidemic response in the US. Scientific advice from CDC and other national public health institutions was ignored ([The Lancet 2020](#)). The [US](#) is the country with the highest number of cases and deaths. Without this unprecedented vacuum in leadership ([NEJM Editors 2020](#)), most of these deaths would have been prevented.

Brazil, which is also not an example of good governance performance, has become the country with the second highest number of deaths in the world.

Partial preparedness (France)

France was partially prepared. During the first national outbreak near Mulhouse, hospitals were overwhelmed. Despite the updated and well-structured pandemic plan (<https://www.gouvernement.fr/risques/plan-pandemie-grippale>), all over the country protective equipment was in short supply; in particular, face masks were sorely lacking after a decision by the Hollande government to greatly reduce the stocks of 1.7 billion protective masks (surgical and FFP2) available in 2009 and considered too expensive to only [145 million surgical masks in 2020](#) (“We are not going to manage mask stocks, it is

expensive, because we have to destroy them every five years. *Nous n'allons pas gérer des stocks de masques, c'est coûteux, parce qu'il faut les détruire tous les cinq ans.*") ([Le Monde 200506](#)).

However, France, thanks to Italy, had an important advantage: time. It had several weeks to learn from the events in Lombardy. When, on the weekend of 21 March, virtually from one day to the next, patients started pouring into the hospitals of the [Greater Paris Region](#), the number of available intensive care unit beds had already increased from 1400 to 2,000 during the preceding week. Furthermore, two years before, in a simulation of a major terrorist attack, France had tested the use of a high-speed [TGV train](#) for transporting casualties. At the height of the COVID epidemic, more than 500 patients were evacuated from epidemic hotspots like Alsace and the Greater Paris area to regions with fewer COVID-19 cases. Specially adapted high-speed trains as well as aircraft were employed, transporting patients as far away as Brittany and the Bordeaux area in the South-West, 600 km from Paris and 1000 km from Mulhouse. The French management of ICU beds was a huge logistical success.

Good virologists, huge lab network, family doctors (Germany)

Germany's fatality rate is lower than in other countries. It is assumed that the main reason for this difference is simply testing. While other countries were conducting a limited number of tests in older patients with severe disease, Germany was doing many more tests that included milder cases in younger people ([Stafford 2020](#)). The more people with no or mild symptoms you test and isolate, the lower the fatality rate and the spread of infection.

Furthermore, in Germany's public health system, SARS-CoV-2 testing is not restricted to a central laboratory as in many other nations but can be conducted at quality-controlled laboratories throughout the country. Thanks to reliable PCR methods that had been developed by the end of January from the [Drosten group](#) at Berlin's Charité ([Corman 2020](#)), within a few weeks the overall capacity reached half a million PCR tests a week. The same low fatality rate is seen in South Korea, another country with high testing rates.

Finally, another important reason for the low mortality in Germany might be the age distribution. During the first weeks of the epidemic, most people became infected during carnival sessions or ski holidays. The majority were younger than 50 years of age. Mortality in this age group is markedly lower than in older people.

As a result of these first-wave distinctive features, the case-fatality rate (CFR) of COVID was 0,7% in Germany, compared with CFRs as high as 9,3% and 7,4%

in Italy and the Netherlands, respectively (Sudharsanan 2020, Fisman 2020). Age distribution of cases may explain as much as 66% of the variation of SARS-CoV-2 cases across countries (Sudharsanan 2020).

Herd immunity? Not yet! (Sweden)

Sweden has never really imposed a lockdown, counting on the population to adopt individual social distancing and other protective measures to curb the transmission of SARS-CoV-2. The price was high (Habib 2020). In October 2020, Sweden had a death rate 10 times higher than Norway and five times higher than Denmark, with most deaths occurring in care homes and immigrant communities. Still worse, Sweden didn't benefit economically of its no-lockdown approach as its economic performance contracted at a similar rate as countries in the rest of Europe (Financial Times, 10 May 2020).

Will the autumn and winter reduce the mortality gap between Sweden and Norway and Denmark? Will Sweden, after accepting many deaths in spring, see fewer of them in the future? Will those who died early reduce the number of deaths seen later? Will a (still low!) level of community immunity help slow down the epidemic in winter? In any case, evaluations of cell phone data show that Swedes traveled much less during the summer than, for example, Norwegians or Danes, so they may have imported less infections from summer vacation hotspots. For a detailed discussion of herd immunity, see Randolph 2020.

Deferred beginning, then major impact (South America)

The first case of COVID-19 in Latin America was reported on 26 February in Brazil and by early April all countries had reported at least one imported case. However, in the initial months of 2020, the number of cases was comparatively low in South America compared to Europe or Asia (Haider 2020). As a matter of fact, the local epidemics took off roughly 4 weeks later than in Europe (see www.worldometers.info/coronavirus).

However, the epidemic accelerated during the month of May when South America became the epicenter of the coronavirus pandemic according to WHO. In September, Latin America, home to around 8% of the world's population, accounted for over a quarter of all confirmed COVID-19 cases and nearly a third of all related deaths. There is, however, wide variation between countries, with Brazil and Mexico having some of the worst epidemics in the world, while Uruguay infection rates are comparable to the best performing countries in Asia or Europe (Taylor 2020).

According to Marcos Espinal and colleagues from WHO, there are several factors in Latin America that make this pandemic more difficult to manage: inequality, belts of poverty surrounding big cities, informal economies, and difficult areas of access. Here, as elsewhere, leadership and sound public health policies made a difference. Both Brazil's and Mexico's presidents have been widely criticized for playing down the threat of COVID-19, not taking action to slow its spread, and suggesting alternative ineffective ways of protection (for example, the use of traditional scarves (?) instead of face masks).

However, other countries have performed much better, managing to keep infections low. For example, Cuba and Costa Rica have enforced strict testing, isolation and quarantine measures. The most successful country so far has been Uruguay that managed, though a mix of effective testing, contact tracing, isolation and quarantine, to keep infection rates very low without generalized lockdowns. The President simply asked, rather than ordered, people to stay home for their own well-being and that of fellow citizens (Taylor 2020).

Splendid isolation (New Zealand, Australia)

Australia, New Zealand, French Polynesia, Fiji, New Caledonia and Papua New Guinea and Oceania are among the least hit areas in the world. Geographically isolated islands or island states should be the ideal candidates for elimination trials. However, even New Zealand, which viewed itself in the post-elimination stage and where public life had returned to near normal (Baker 2020), was suddenly called back into COVID-19 reality when new cases were discovered in August 2020.

In Australia, transmission was initially driven by multiple SARS-CoV-2 importations by returned international travelers which accounted for over half of locally acquired cases (Seemann 2020). However, on 20 June, the State of Victoria reported a spike in community transmitted cases, apparently following lax implementation of quarantine measures, that resulted in a large outbreak with more than 20,000 cases and 800 deaths and the imposition of strict lockdown measures in the State and a night curfew in Melbourne. An easing of restrictions only started mid-September, following a major decrease in the number of new cases.

Both Australia and New Zealand have considered a strategy of COVID-19 elimination, i.e. the absence of sustained endemic community transmission in the country. The recent outbreaks have raised the question of whether elimination is a reasonable goal (Hewyood 2020). The elimination of any infectious disease is an ambitious objective, requiring strong public health measures and substantial resources. In principle, a zero-case scenario of not less than three months would be the condition for declaring a state or country SARS-

CoV-2-free. Then, strict travel and border restrictions and quarantine measures must be implemented over a prolonged period, since the virus continues to spread around the world. It looks like international travel to New Zealand and Australia may continue to be banned for quite some time.

Africa: The unknown (?) outcome

The transmissibility of SARS-CoV-2, combined with the scarcity of crucial health equipment and facilities and the challenges of implementing wide-spread case isolation ([Wells 2020](#)), was supposed to result in a devastating impact of COVID-19 on African countries. These predictions have not materialized. (To put the area into focus, remember that Europe without Russia has a surface of roughly 6 million km², Africa has 30 million km². That should explain by itself that the burden and outcomes associated with COVID-19 in Africa shows substantial variations across African countries [[Twahirwa 2020](#)]. There is no ‘one’ Africa.)

Some official figures are certainly underestimates, voluntary or not, due to regional difficulties in reporting. In some cities, such as [Kano](#), Nigeria, major outbreaks may already be underway. The [New York Times](#) reported on 17 May, “so many doctors and nurses have been infected with SARS-CoV-2 that few hospitals are now accepting patients”. Gravediggers are working overtime. In Mogadishu, Somalia, officials say burials had tripled, according to the same report. In Tanzania, the US embassy has warned of the risk of “exponential growth” of COVID-19 cases in the country, adding that hospitals were “overwhelmed” ([The Guardian](#), 19 May).

However, there has been no COVID-19 explosion in Africa. Has time come to hypothesize an “African exception”? It is probably too early to say but demographics might explain in part the difference. In the Democratic Republic of the Congo and Malawi, for instance, only 2-3% of the population is older than 65 years ([Kalk 2020](#)), in sharp contrast to Europe at 20,5% or Lombardy at 26%. If 65-year-old SARS-CoV-2 infected individuals are 100 times more likely to die from COVID-19 than a 25-year-old, we should expect two different epidemics. Simply, the age pyramid might make the difference.

The SARS-CoV-2 pandemic: Past and Future

Natural course of a pandemic

The COVID-19 epidemic started in Wuhan, in Hubei province, China, and spread within 30 days from Hubei to the rest of mainland China, to neighboring countries (in particular, South Korea, Hong Kong and Singapore) and west to Iran, Europe and the Americas. The first huge outbreaks occurred in regions with cold winters (Wuhan, Iran, Northern Italy, the Alsace region in France).

Fifty years ago, the course of the COVID-19 pandemic would have been different, with slower global spread but high burden due to limited diagnostic and therapeutic capacities and no option of nation-wide lockdowns (see also a report of the influenza pandemics in 1957 and 1968: [Honigsbaum 2020](#)). According to one (controversial) simulation, in the absence of interventions and with a mortality rate of around 0.5%, without interventions COVID-19 would have resulted in 7.0 billion infections and 40 million deaths globally during the first year ([Patrick 2020](#)). The peak in mortality (daily deaths) would have been observed approximately 3 months after the beginning of local epidemics. Another model predicted that 80% of the US population (around 260 million people) would have contracted the disease. Of those, 2.2 million Americans would have died, including 4% to 8% of those over age 70 ([Ferguson 2020](#)). In Germany alone, the SARS-CoV-2 pandemic could have resulted in 730,000 deaths ([Barbarossa 2020](#)) and in 500,000 deaths each in France, Italy, Spain and the UK.

The 2020 Lockdowns

Fortunately, for now, the world has been spared from a freely circulating SARS-CoV-2. If humanity can change the climate, why shouldn't we be able to change the course of a pandemic? Although economists warned that [unemployment](#) could surpass the levels reached during the [Great Depression in the 1930s](#), at first, almost all governments considered saving hundreds of thousands lives more important than avoiding a massive economic recession. First in China, six weeks later in Italy and another a week later in most Western European countries, more recently in the US and in many other countries in the world, unprecedented experiments of gigantic dimensions were started: ordering entire regions or the whole nation to lockdown. By the first week of April, 4 billion people worldwide were under some form of lockdown — more than half of the world's population. Lockdowns in Europe were generally less strict than in China, allowing the continuation of essential services and industries and the circulation of people when justified.

People were generally compliant to mandatory stay-at-home orders, even in the US. Based on location data from mobile devices, in 97.6% of US counties these orders were associated with decreased median population movement ([Moreland 2020](#)). Lockdowns were generally also well accepted. During the week of May 5–12, 2020, a survey among 2402 adults in New York City and Los Angeles found widespread support of stay-at-home orders and non-essential business closures and a high degree of adherence to COVID-19 mitigation guidelines ([Czeisler 2020](#)). In New York City, SARS-CoV-2 prevalence varied substantially between boroughs between 22 March and 3 May 2020 (for example, Manhattan: 11,3%; South Queens: 26,0%). These differences in prevalence correlate with antecedent reductions in commuting-style mobility between the boroughs. Prevalence was lowest in boroughs with the greatest reductions in morning movements out of and evening movements into the borough ([Kissler 2020](#)).

Lockdowns were also successful in slowing down the pandemic. According to one study, between 12 and 15 million individuals in Europe had been infected with SARS-CoV-2 by May 4th, representing between 3.2% and 4.0% of the population ([Flaxman June 2020](#)). Projected percentages of the total population infected were for Austria 0,76%, Belgium 8,0%, Denmark 1,0%, France 3,4%, Germany 0,85%, Italy 4,6%, Norway 0,46%, Spain 5,5%, Sweden 3,7%, Switzerland 1,9% and the UK 5,1%. In South America, lockdowns were successful, too, although they worked best among the wealthy and less well among the less wealthy who had to choose between the risk of dying from COVID or dying from hunger.

There is no real pandemic in Africa, a never-ending wave in the Americas, and now a second wave in Europe. The worst may be yet to come ([The Lancet 2020](#)) with more people dying and every death leaving 10 more people mourning a grandparent, parent, sibling, spouse, or child ([Verderly 2020](#)). Will the winter SARS-CoV-2 pandemic follow the scenario of the 1918 influenza pandemic ([Horton 2020](#))?

In the French Bouches-du-Rhône department which includes Marseille, the first signs of the second wave were detected in wastewater on July 13¹. Three weeks later, the first post-lockdown rise in new SARS-CoV-2 infections was seen in young adults 20 to 29 years old, and again a few weeks later, infection

¹ SARS-CoV-2 can be detected in wastewater using RT-qPCR. In one study, the total load of gene equivalents in wastewater correlated with the cumulative and the acute number of COVID-19 cases reported in the respective catchment areas [[Westhaus 2020](#)]. Note that wastewater is no route for SARS-CoV-2 transmission to humans! All replication tests were negative tests.

rates increased in older age groups. In Spain (NCOMG 2020), Switzerland (see Figure 1) and other European countries, the second wave looked equally triggered mostly by transmission among young adults in leisure venues such as bars, restaurants, discos or clubs during the summer 2020.

80+	2,7	2,9	5,8	9,2	17,1	22,5	13,5	17,1	31,0	66,5
70 - 79	3,9	4,2	3,8	5,8	8,2	14,2	14,8	14,5	22,0	57,8
60 - 69	7,4	9,7	10,9	11,1	14,4	21,5	23,8	17,4	31,6	75,4
50 - 59	12,3	12,8	12,8	17,5	25,0	28,6	32,0	29,9	40,9	101,9
40 - 49	11,8	16,0	19,4	24,2	29,2	38,8	40,4	29,5	43,8	107,3
30 - 39	18,2	25,6	30,7	34,3	41,9	43,3	46,1	36,6	59,4	126,7
20 - 29	29,3	53,3	63,8	63,2	68,7	71,4	66,0	46,0	74,3	183,7
10 - 19	16,1	21,7	26,3	31,0	26,6	37,0	40,3	21,7	30,1	80,1
0 - 9	2,2	3,3	3,4	4,4	4,8	2,3	1,7	1,7	3,1	6,5
	03.08.	10.08.	17.08.	24.08.	31.08.	07.09.	14.09.	21.09.	28.09.	05.10.

Figure 1. Weekly positive SARS-CoV-2 tests in Switzerland by age group (August 3 through October 5). Source: SRF, *So entwickeln sich die Corona-Zahlen in der Schweiz* (<https://www.srf.ch/news/schweiz/coronavirus-so-entwickeln-sich-die-corona-zahlen-in-der-schweiz>; accessed 12 October 2020).

Let's briefly discuss

- Measuring the epidemic
- Herd immunity: Not yet
- Vaccines: Be patient
- 'Variolation' – Finding of the year?
- Protection: People at risk
- Prevention: Testing, tracing, isolating
- Curfews

Measuring the epidemic

In the current second European wave, the number of newly diagnosed SARS-CoV-2 cases and the [positive rate of PCR tests](#) are certainly useful markers for the evolution of national epidemics; however, the number of hospitalizations and, most importantly, the number of new admissions to intensive care units (ICU) and deaths are the crucial figures in terms of disease burden (Figure 2 and 3).

Note that all these markers have limitations. For example, the number of positive cases identified are related to the number of tests performed and testing strategies. Hospital admissions also have limitations (hospital admission criteria may change from place to place and be modified over time) and can be influenced by, for example, the availability of quality home-based care or the collapse of an overburdened health system. In addition, many governments are not publicly providing numbers of daily hospital admissions and discharges ([Garcia-Basteiro 2020](#)).

In anticipating local epidemics, politicians should prepare for the worst, at least until spring 2021. An important feature of this second wave of infections is its widespread nature, as opposed to earlier, more localized outbreaks (e.g. northern Italy, Madrid, Spain or Mulhouse, France.) More populated and better-connected municipalities were generally affected earlier by the SARS-CoV-2 epidemic, and less populated municipalities at a later stage of the epidemic ([de Souza 2020](#)). However, relaxation of mitigation measures leading to a resumption of “normal” diffusion may initially appear to have few negative effects, only to lead to deadly outbreaks weeks or months later ([Thomas 2020](#)). Public health messaging may need to stress that apparent lulls in disease progress are not necessarily indicators that the threat has subsided, and that areas “passed over” by past outbreaks could be impacted at any time.

Herd immunity: Not yet

Herd immunity, the notion introduced to a wider public by a foolish politician, may not be on the agenda for a long time. Herd immunity, also known as *indirect protection*, *community immunity*, or *community protection*, refers to the protection of susceptible individuals against an infection when a sufficiently large proportion of immune individuals exist in a population ([Omer 2020](#)). As for now, not a single country is anywhere close to reaching herd immunity. Even in past hotspots like Wuhan, the prevalence of SARS-CoV-2 IgG positivity was 9.6% among 1021 people applying for a permission (the SARS-CoV-2 nucleic acid test needed to be negative) ([Wu X 2020](#)). A French study projected 2.8 million or 4.4% (range: 2.8–7.2) prevalence of infections in France. In Los Angeles, the prevalence of antibodies was 4.65% ([Sood 2020](#)). (And even

this low number may be biased because symptomatic persons may have been more likely to participate.) A nationwide coronavirus antibody study in Spain showed that about 5% of the population had contracted the virus. These infection rates are clearly insufficient to avoid a second wave of a SARS-CoV-2 epidemic (Salje 2020). Achieving herd immunity without overwhelming hospital capacity would require an unlikely balancing of multiple poorly defined forces (Brett 2020).

Vaccines: Be patient

Some fools – politicians and experts alike – announced efficient and safe vaccines two months before Christmas 2020. Reality will see such thoroughly tested vaccines delivered to the first groups of vaccinees (i.e., health care workers) way into 2021, and nobody should expect vaccines to have a noticeable impact on the SARS-CoV-2 pandemic before the end of next year. In the meantime, people will need to be patient and look for alternative ways of protection.

‘Variolation’ – Finding of the year?

Reducing the viral SARS-CoV-2 inoculum might not only reduce the probability of infection but also favor an asymptomatic infection while still generating immunity. This suggestion (Bielecki 2020) was later further developed (Ghandi 2020; see also the comments to the paper by Rasmussen 2020, Brosseau 2020): if facial masking may help in reducing the size of the viral inoculum, universal facial masking might ensure that a greater proportion of new infections are asymptomatic. If universal masking could be proved to be a form of ‘variolation’ (inoculation), it would be an additional argument in favor of strict mask wearing.

Protecting people at risk

Protecting those at higher risk of SARS-CoV-2 infection, for example the elderly and healthcare workers (Nguyen 2020), will continue to be the highest priority over the coming months. Specific population groups might be at higher risk too. In the UK and the US, Black, Asian, and minority ethnic health care workers are at especially high risk of SARS-CoV-2 infection, with at least a fivefold (!) increased risk of COVID-19 compared with the non-Hispanic white general community. The infection rate is also higher in the most poor and vulnerable areas, thus emphasizing existing inequalities (Grasso 2020: COVID of the rich, COVID of the poor).

In a cross-sectional study of 396 pregnant New York City residents, large household membership, household crowding, and low socioeconomic status

were associated with a 2-3 fold higher risk of infection (Emeruwa 2020). American Indian and Alaska Native (AI/AN) persons, too, appear to be disproportionately affected by the COVID-19 pandemic. In one study, the overall COVID-19 incidence among AI/AN persons was 3.5 times that among white persons (594 per 100,000 AI/AN population compared with 169 per 100,000 white population) (Hatcher 2020).

Prevention: Testing, tracing, isolating

Screening, case investigation, contact tracing, and isolation of infected persons is paramount during periods of community transmission. In a random sample of 350 adults aged ≥ 18 years who had positive RT-PCR in outpatient and inpatient settings at 11 US academic medical centers, only 46% were aware of recent close contact with someone with COVID-19, most commonly a family member (45%) or a work colleague (34%) (Tenforde 2020).

Testing presents numerous challenges (Clapham 2020), but the more people you test for SARS-CoV-2, the better. In a worldwide cross-sectional study (Liang LL 2020), COVID-19 mortality was

- Negatively associated with
 - Test number per 100 people
 - Government effectiveness score
 - Number of hospital beds
- Positively associated with
 - Proportion of population aged 65 or older
 - Transport infrastructure low quality score

Testing was a major limiting factor in assessing the extent of SARS-CoV-2 transmission during its initial spread into the US (Perkins 2020). After a national emergency was declared, fewer than 10% of locally acquired, symptomatic infections in the US were detected over a period of a month. This gap in surveillance during a critical phase of the epidemic resulted in a large, undetected reservoir of infections by early March. Other countries did better. Citywide mass nucleic acid testing of SARS-CoV-2 for all citizens is possible as shown in Wuhan city (14 May to 1 June 2020). The results are sometimes meager, revealing just 6 persons who test positive for SARS-CoV-2 (0,006% of 107,662 residents around the Huanan Seafood Market), but are able to suffocate a nascent epidemic (Jingwen L 2020).

It is important to recognize that despite aggressive efforts by health departments, many COVID-19 patients do not report contacts, and many contacts cannot be reached (Lash 2020). Staff members in North Carolina, US have in-

investigated 5514 (77%) persons with COVID-19 in Mecklenburg County and 584 (99%) in Randolph Counties: during periods of high COVID-19 incidence, 48% and 35% of patients reported no contacts, and 25% and 48% of contacts were not reached. Median interval from index patient specimen collection to contact notification was 6 days. Some countries are obviously better prepared for mass testing than others and capable of performing 9 million tests in 5 days after the detection of 12 cases in a previously COVID-free area (Vidal Liy 2020 + BBC).

Curfews

Lockdowns are effective but frighteningly costly. The spring lockdown cost most countries around 10% of their PIB with unforeseeable economic, political and also health consequences; in exchange, they can “flatten the curve” and did succeed in keeping seroprevalence rates low, somewhere between 1% and 10%. General lockdowns are clearly not a viable model for the future.

Might curfews be a less costly alternative, both economically and socially? In French Guiana, an overseas *département*, a combination of curfews and targeted lockdowns in June and July 2020 was sufficient to avoid saturation of hospitals. On weekdays, residents were first ordered to stay at home at 11 p.m., then at 9 p.m., later at 7 p.m., and finally at 5 p.m. On weekends, everyone had to stay at home from 1 p.m. on Saturday (Andronico 2020). Whether curfews can be successfully adapted to other areas than French Guiana, is not known. French Guiana is a young territory with a median age of 25 years and the risk of hospitalization following infection was only 30% that of France. About 20% of the population had been infected with SARS-CoV-2 by July 2020 (Andronico 2020). Following Belgium and Germany, France has just implemented now its night curfew in Paris and a few other major cities. Be prepared to see more curfews orders over the coming six months.

Outlook

How long will SARS-CoV-2 stay with us? How long will it be before we return to pre-COVID-19 ‘normalcy’? For how long will a combination of physical distancing, enhanced testing, quarantine, and contact tracing be needed? Historical evidence from prior influenza pandemics indicates that pandemics tend to come in waves over the first 2–5 years as population immunity builds-up (naturally or through vaccination) and that this is the most likely trajectory for SARS-CoV-2 (Petersen 2020). Even vaccines are not expected to have a substantial impact on the pandemic before 2022, if ever. In the meantime, classical infection control measures are the only way to reduce the number of infections and avoid healthcare systems from breaking down, leaving patients

with other morbidities – common emergencies and surgery, cancer treatment, management of patients with chronic diseases – stranded and abandoned in a medical no-man’s land.

Summer of 2020 has shown that the post-lockdown epidemic dynamic was driven by younger adults with gradual ‘spill-over’ into older age groups. However, the formula ‘young adults -> parents -> grandparents -> death’ shall not be used as a simplistic model for the European second wave. SARS-CoV-2 is introduced and spread in communities via all conceivable routes. It is therefore important to define the behaviors than can minimize the risk of local lockdowns and economic hardship.

In situations of intense SARS-CoV-2 community transmission, the prevention triad is simple:

1. Stop people from meeting each other in large gatherings.
2. If they MUST meet, have them wear face masks.
3. In any case reduce the time infected or suspected infectious people meet any other people at all: test as much as possible, isolate cases quickly and track the close contacts.

In transmission hotspots, restrictive social-distancing measures will need to be combined with widespread testing and contact tracing to slow down the ongoing pandemic ([Giordano 2020](#) + less realistic, [Peto 2020](#)). People should concentrate on the essential activities of providing food and shelter as well as continuing their job, school and university activities. All ‘après-work’ and ‘après-school’ activities should be reduced to a minimum (no evening bars, no night life). In such social slowdowns, people will need to avoid prolonged meetings with people from outside their inner-core “friends-and-family-bubble”, in particular social events which bring people from many different families together (marriages, funerals, religious events). Even inside the inner-core “friends-and-family-bubble”, meetings should be restricted to a handful of people. Economically, a social slowdown implies the temporary closure of places where foreigners, strangers or simply unacquainted people meet: discos, amusement parks, bars, restaurants, brothels and many more. In a situation of intense SARS-CoV-2 community transmission, strangers must not come into contact.

Coronaviruses have come a long way ([Weiss 2020](#)) and will stay with us for a long time. Questions abound: When will we move freely around the world as we did before? Will air traffic return to pre-COVID-19 levels by 2024 or only later? Will we be inclined to plan vacations nearer to home rather than on the other side of the globe? Will we wear face masks for years? Will there be any nightlife event with densely packed people dancing and shouting and drink-

ing in any city in the world anytime soon? Nobody knows. We only know that old and obese countries are hard hit and young and slim countries are relatively spared.

The French have an exquisitely precise formula to express unwillingness for living in a world you do not recognize: “Un monde de con!” Fortunately, we will be able to walk out of this *monde de con* thanks to a scientific community which is larger, stronger, and faster than at any time in history. (BTW, should politicians who are skeptical of science be ousted out of office? Yes, please! It is about time!) As of today, we do not know how long-lasting, how intense, and how deadly this pandemic will be. We are walking on moving ground and, in the coming months and years, we will need to be flexible, resilient, and inventive, looking for and finding solutions nobody would have imagined just months ago. Sure enough though, science will lead the way out. If we could leap five years into the future and read the story of COVID-19, we would not believe our eyes.

New References (5th Edition)

The following pages add short comments to the papers published since the previous edition (June-October). The comments are from <https://covidreference.com/daily-science>. After a selection of the best articles, find the new articles of the 5th edition grouped according to the outline of the chapter (page 55). The complete list of references starts at page 78.

Top Articles

Leadership vacuum

NEJM Editors. **Dying in a Leadership Vacuum.** N Engl J Med 2020; 383:1479-1480. Full-text: <https://www.nejm.org/doi/full/10.1056/NEJMe2029812>

SARS-CoV-2 and the COVID-19 pandemic became a test of leadership. With no good options to combat a novel pathogen, countries were forced to make hard choices about how to respond. In the United States, the leaders have failed that test.

“Variolation”?

Bielecki M, Züst R, Siegrist D, et al. **Social distancing alters the clinical course of COVID-19 in young adults: A comparative cohort study.** Clin Inf Dis, June 29, 2020. Full-text: <https://doi.org/10.1093/cid/ciaa889>

Gandhi M, Rutherford GW. **Facial Masking for Covid-19 — Potential for “Variolation” as We Await a Vaccine.** NEJM September 8, 2020. Full-text: <https://doi.org/10.1056/NEJMp2026913>

Reducing the viral SARS-CoV-2 inoculum might not only reduce the probability of infection but also favor an asymptomatic infection while still generating immunity. This suggestion by Michel Bielecki et al. in June 2020 (Bielecki 2020) was later developed by Monica Gandhi and George W. Rutherford (Ghandi 2020). If facial masking may help reducing the size of the viral inoculum, universal facial masking might ensure that a greater proportion of new infections are asymptomatic. If universal masking could be proved to be a form of “variolation” (inoculation), it would be a giant leap to pandemic control.

SARS-CoV-2 Emergence in Europe and North America

Worobey M, Pekar J, Larsen BB, et al. **The emergence of SARS-CoV-2 in Europe and North America.** Science 2020, published 10 September. Full-text: <https://doi.org/10.1126/science.abc8169>

Despite the early successes in containment, SARS-CoV-2 eventually took hold in both Europe and North America during the first two months of 2020: first in Italy around the end of January, then in Washington State around the beginning of February, and followed by New York City later that month (Worobey 2020; see also Figure 6).

Brazil

Candido DS, Claro M, de Jesus JG, et al. **Evolution and epidemic spread of SARS-CoV-2 in Brazil.** Science 23 Jul 2020:eabd2161. Full-text: <https://doi.org/10.1126/science.abd2161>

Sequencing of hundreds of genomes showed that more than 100 international virus introductions in Brazil with 76% of Brazilian strains falling into three clades that were introduced from Europe between 22 February and 11 March 2020 (Candido 2020).

Mumbai, India

Kolthur-Seetharam U, Shah D, Shastri J, Juneja S, Kang G, Malani A, Mohanan M, Lobo GN, Velhal G, Gomare M. **SARS-CoV2 Serological Survey in Mumbai by NITI-BMC-TIFR**. Tata Institute of Fundamental Research (TIFR) 2020, published 29 June. Full-text: <https://www.tifr.res.in/TSN/article/Mumbai-Serosurvey%20Technical%20report-NITI.pdf>

In a cross-sectional survey in Mumbai, India, the prevalence of SARS-CoV-2 infection in three areas in Mumbai (called ‘wards’) was around 57% in the slum areas of Chembur, Matunga and Dahisar, and 16% in neighboring non-slums (Kolthur-Seetharam 2020). If these data are confirmed, some Mumbai areas would soon reach herd immunity and could return to a pre-COVID way of life. For many countries in the world, this would be the best piece of news since the beginning of the pandemic.

Frontline healthcare workers: US

Self WH, Tenforde MW, Stubblefield WB, et al. **Seroprevalence of SARS-CoV-2 Among Frontline Health Care Personnel in a Multistate Hospital Network — 13 Academic Medical Centers, April–June 2020**. MMWR. Full-text: <http://dx.doi.org/10.15585/mmwr.mm6935e2>

Many cases appear to go undetected: among 3,248 HCWs who routinely cared for COVID-19 patients in 13 US academic medical centers from February 1, 2020, 194 (6%) had evidence of previous SARS-CoV-2 infection, with considerable variation by location that generally correlated with community cumulative incidence. Among 194 participants who had SARS-CoV-2 antibodies, 56 (29%) did not recall any symptoms consistent with an acute viral illness in the preceding months and 133 (69%) did not have a previous positive test result demonstrating an acute SARS-CoV-2 infection. Prevalence of SARS-CoV-2 antibodies was lower among personnel who reported always wearing a face covering while caring for patients (6%), compared with those who did not (9%).

Frontline healthcare workers: London

Houlihan CF, Vora N, Byrne T, et al. **Pandemic peak SARS-CoV-2 infection and seroconversion rates in London frontline health-care workers**. Lancet July 09, 2020. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31484-7](https://doi.org/10.1016/S0140-6736(20)31484-7)

High-risk frontline healthcare workers (HCV) are really at high risk. In a prospective cohort study in an acute National Health Service hospital trust in London, 25% of HCWs were already seropositive at enrolment (26 March to 8 April) and a further 20% became seropositive within the first month of follow-

up (Houlihan 2020). Most infections occurred between March 30 and April 5, the week with the highest number of new cases in London.

School Openings

Cheng SY, Wang J, Shen AC, et al. **How to Safely Reopen Colleges and Universities During COVID-19: Experiences From Taiwan.** Ann Int Med 2020, Jul 2. Full-text: <https://doi.org/10.7326/M20-2927>

Taiwan is one of the few countries where schools are functioning normally. To secure the safety of students and staff, the Ministry of Education in Taiwan established general guidelines, including a combination of strategies such as – our future? - active campus-based screening and access control; school-based screening and quarantine protocols; student and faculty quarantine when warranted; mobilization of administrative and health center staff; regulation of dormitories and cafeterias; and reinforcement of personal hygiene, environmental sanitation, and indoor air ventilation practices (Cheng SY 2020). Depressing (“un monde de con”), but probably necessary.

Second Wave

NCOMG. The national COVID-19 outbreak monitoring group. **COVID-19 outbreaks in a transmission control scenario: challenges posed by social and leisure activities, and for workers in vulnerable conditions, Spain, early summer 2020.** Eurosurveillance Volume 25, Issue 35, 03/Sep/2020. Full-text: <https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.35.2001545>

From mid-June to 2 August, excluding single household outbreaks, 673 outbreaks were notified in Spain (NCOMG 2020). There were two main settings where over 55% of active outbreaks (303/551) and over 60% (3,815/6,208) of active outbreak cases originated: First, social settings such as family gatherings or private parties (112 outbreaks, 854 cases), followed by those linked to leisure venues such as bars, restaurants, or clubs (34 outbreaks, over 1,230 cases). Second, occupational settings (representing 20% of all active outbreaks), mainly among workers in the fruit and vegetable sector (31 outbreaks and around 500 cases) and workers at slaughterhouses or meat processing plants (12 outbreaks and around 360 cases).

Rigorous wildlife disease surveillance

Watsa M. **Rigorous wildlife disease surveillance.** Science 10 Jul 2020, 369: 145-147. Full-text: <https://doi.org/10.1126/science.abc0017>

Emerging infectious diseases (EID) associated with the wildlife trade remain the largest unmet challenge of current disease surveillance efforts. International or national conventions on pathogen screening associated with animals, animal products or their movements are urgently needed (Watsa 2020). Internationally recognized standard for managing wildlife trade on the basis of known disease risks should be established.

More Articles

Introduction

McNeil Jr DG. **A Viral Epidemic Splintering Into Deadly Pieces.** The New York Times, 29 July 2020. Full-text: <https://www.nytimes.com/2020/07/29/health/coronavirus-future-america.html>

Some articles in the lay press are outstanding documents, and a few are better than two thirds of published and pre-published scientific articles about COVID-19. Read these 4,000 words thoughtfully put down by Donald G. McNeil Jr. If you don't read it now, read it on the weekend.

Adam D. **A guide to R — the pandemic's misunderstood metric.** Nature News. 03 July 2020. Full-text: <https://www.nature.com/articles/d41586-020-02009-w>

Nice article about what R, the reproduction number, can and can't tell us about managing COVID-19 (Adam 2020). Politicians seem to have embraced R with enthusiasm but it's far more important to watch for clusters of cases and to set up comprehensive systems to test people, trace their contacts and isolate those infected, than to look at R.

Yu X, Wei D, Chen Y, et al. **Retrospective detection of SARS-CoV-2 in hospitalized patients with influenza-like illness.** Emerging Microbes & Infections 2020, Full-text: <https://doi.org/10.1080/22221751.2020.1785952>

There was no 'stealthy' SARS-CoV-2 transmission before the outbreak in Wuhan, China. In a retrospective screening for SARS-CoV-2 RNA in 1,271 nasopharyngeal swab samples, as well as the prevalence of IgM, IgG, and total antibodies against SARS-CoV-2 in 357 matched serum samples collected from hospitalized patients with influenza-like illness between December 1, 2018 and March 31, 2020 in Shanghai Ruijin Hospital, the onset date of the earliest COVID-19 case was January 25 (Yu X 2020).

Worobey M, Pekar J, Larsen BB, et al. **The emergence of SARS-CoV-2 in Europe and North America.** Science 2020, published 10 September. Full-text: <https://doi.org/10.1126/science.abc8169>

Despite the early successes in containment, SARS-CoV-2 eventually took hold in both Europe and North America during the first two months of 2020: first in Italy around

the end of January, then in Washington State around the beginning of February, and followed by New York City later that month (Worobey 2020; see also Figure 6).

Dawood FS, Ricks P, Njie GJ, et al. **Observations of the global epidemiology of COVID-19 from the prepandemic period using web-based surveillance: a cross-sectional analysis.** *Lancet Infect Dis* 2020, published 29 July. Full-text: [https://doi.org/10.1016/S1473-3099\(20\)30581-8](https://doi.org/10.1016/S1473-3099(20)30581-8)

Fatimah Dawood and colleagues describe the global spread of SARS-CoV-2 and characteristics of COVID-19 cases and clusters *before* WHO declared COVID-19 as a pandemic on 11 March 2020 (i.e., pre-pandemic). They identified cases of COVID-19 from official websites, press releases, press conference transcripts, and social media feeds of national ministries of health or other government agencies. Cases with travel links to China, Italy, or Iran accounted for almost two-thirds of the first reported COVID-19 cases from affected countries (Dawood 2020). There were many clusters of household transmission among early cases; however, clusters in occupational or community settings tended to be larger.

Deng X, Gu W, Federman S, et al. **Genomic surveillance reveals multiple introductions of SARS-CoV-2 into Northern California.** *Science* 08 Jun 2020. Full-text: <https://doi.org/10.1126/science.abb9263>

Early genomic surveillance revealed the cryptic introduction of at least 7 different SARS-CoV-2 lineages into California (Deng X 2020).

Candido DS, Claro M, de Jesus JG, et al. **Evolution and epidemic spread of SARS-CoV-2 in Brazil.** *Science* 23 Jul 2020:eabd2161. Full-text: <https://doi.org/10.1126/science.abd2161>

Sequencing of hundreds of genomes showed that more than 100 international virus introductions in Brazil with 76% of Brazilian strains falling into three clades that were introduced from Europe between 22 February and 11 March 2020 (Candido 2020).

Seroprevalence

ITALY

Sabbadini LL, Romano MC, et al. **[First results of the seroprevalence survey about SARS-CoV-2] (Primi risultati dell'indagine di sieroprevalenza sul SARS-CoV-2).** Italian Health Ministry and National Statistics Institute 2020, published 3 August. Full-text (Italian): <https://www.istat.it/it/files//2020/08/ReportPrimiRisultatiIndagineSiero.pdf>

According to a representative study by the Italian Ministry of Health (64,000 participants), 1.5 million people (2.5% of the population) had SARS-CoV-2 antibodies during the study period from May 25 to July 15 (Sabbadini 2020). This figure is higher than the currently reported 250,000 cases. If these figures are true, the *infection fatality rate* (IFR, the proportion of deaths among all the infected individuals) in Italy would be

2.3% (35,000 deaths/1,500,000 infections). This is higher than in other European countries and needs to be addressed in future studies.

Bassi F, Arbia G, Falorsi PD. **Observed and estimated prevalence of Covid-19 in Italy: How to estimate the total cases from medical swabs data.** *Sci Total Environ.* 2020 Oct 8:142799. PubMed: <https://pubmed.gov/33066965>. Full-text: <https://doi.org/10.1016/j.scitotenv.2020.142799>

A national survey in Italy from May to July 2020 (see previous article) found a nationwide seropositivity rate of 2.5% (Sabbadini 2020). Insiders never believed these figures and favored a seropositivity rate of 5-10% like in Spain or in France. Now we have a new estimate of COVID-19 prevalence in Italy by Francesca Bassi and colleagues: 9%, corresponding to almost 6 million Italians.

Percivalle E, Cambiè G, Cassaniti I, et al. **Prevalence of SARS-CoV-2 specific neutralising antibodies in blood donors from the Lodi Red Zone in Lombardy, Italy, as at 06 April 2020.** *Euro Surveill.* 2020 Jun;25(24):2001031. PubMed: <https://pubmed.gov/32583766>. Full-text: <https://doi.org/10.2807/1560-7917.ES.2020.25.24.2001031>

In the highly affected “Lodi Red Zone” in Italy (an area of 169 km², including 10 municipalities and 51,500 inhabitants, which went into lockdown in February 2020), 91 of 390 blood donors (23%) aged 19–70 years were antibody positive (Percivalle 2020).

SPAIN

Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al. **Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study.** *The Lancet* 2020, July 06, 2020. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31483-5](https://doi.org/10.1016/S0140-6736(20)31483-5)

The vast majority (95%) of the Spanish population is seronegative, even in hotspot areas. In a nationwide, representative study, 61,075 participants were tested. Seroprevalence was 5.0% (95% CI 4.7–5.4) by the point-of-care test and 4.6% (4.3–5.0) by immunoassay, with a lower seroprevalence in children younger than 10 years (< 3.1% by the point-of-care test) (Pollán 2020). There was high geographical variability, with higher prevalence around Madrid (> 10%) and lower in coastal areas (< 3%).

Soriano V, Meiriño R, Corral O, Guallar MP. **SARS-CoV-2 antibodies in adults in Madrid, Spain.** *Clin Infect Dis.* 2020 Jun 16:ciaa769. PubMed: <https://pubmed.gov/32544951>. Full-text: <https://doi.org/10.1093/cid/ciaa769>

Even in regions that were hard hit by the first SARS-CoV-2 wave (like the Madrid area with 65,000 confirmed cases and 9,000 deaths up to May 10th), only roughly 11% of adults had SARS-CoV-2 antibodies at the time of lockdown release on May 10th (Soriano 2020).

US

Ng DL, Goldgof GM, Shy BR, et al. **SARS-CoV-2 seroprevalence and neutralizing activity in donor and patient blood.** Nat Commun. 2020 Sep 17;11(1):4698. PubMed: <https://pubmed.gov/32943630>. Full-text: <https://doi.org/10.1038/s41467-020-18468-8>

In April 2020, SARS-CoV-2 seroprevalence was low in the San Francisco Bay Area (0.26% in 387 hospitalized patients; 0.1% in 1,000 blood donors) (Ng DL 2020). Charles Y. Chiu, Dianna Ng and colleagues also describe the longitudinal dynamics of immunoglobulin-G (IgG), immunoglobulin-M (IgM), and *in vitro* neutralizing antibody titers in COVID-19 patients. The median time to seroconversion ranged from 10.3–11.0 days for these 3 assays. The authors provide evidence that seropositive results using SARS-CoV-2 anti-nucleocapsid protein IgG and anti-spike IgM assays are generally predictive of *in vitro* neutralizing capacity.

Havers FP, Reed C, Lim T, et al. **Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23–May 12, 2020.** JAMA Intern Med. 2020 Jul 21. PubMed: <https://pubmed.gov/32692365>. Full-text: <https://doi.org/10.1001/jamainternmed.2020.4130>

In a cross-sectional study, the proportion of seropositive persons ranged from 1.0% in the San Francisco Bay area (collected April 23–27) to 6.9% of persons in New York City (collected March 23–April 1) (Havers 2020). The estimated number of SARS-CoV-2 infections is around 10 times the number of reported cases.

Moscola J, Sembajwe G, Jarrett M, et al. **Prevalence of SARS-CoV-2 Antibodies in Health Care Personnel in the New York City Area.** JAMA 2020, published 6 August. <https://doi.org/10.1001/jama.2020.14765>

Health care personnel (HCP) have a high exposure risk for SARS-CoV-2 infection. In New York, the prevalence of SARS-CoV-2 was 13.7 (5523 of 40,329 HCWs tested) which was similar to that among adults randomly tested in New York State (14.0%). (Moscola 2020).

INDIA

Kolthur-Seetharam U, Shah D, Shastri J, Juneja S, Kang G, Malani A, Mohanan M, Lobo GN, Velhal G, Gomare M. **SARS-CoV2 Serological Survey in Mumbai by NITI-BMC-TIFR.** Tata Institute of Fundamental Research (TIFR) 2020, published 29 June. Full-text: <https://www.tifr.res.in/TSN/article/Mumbai-Serosurvey%20Technical%20report-NITI.pdf>

In a cross-sectional survey in Mumbai, India, the prevalence of SARS-CoV-2 infection in three areas in Mumbai (called ‘wards’) was around 57% in the slum areas of Chembur, Matunga and Dahisar, and 16% in neighboring non-slums (Kolthur-Seetharam 2020). If these data are confirmed, some Mumbai areas would soon reach herd immun-

ity and could return to a pre-COVID way of life. For many countries in the world, this would be the best piece of news since the beginning of the pandemic.

FAROE ISLANDS

Petersen MS, Strøm M, Christiansen DH, Fjallsbak JP, Eliassen EH, Johansen M, et al. **Seroprevalence of SARS-CoV-2-specific antibodies, Faroe Islands.** Emerg Infect Dis 2020 Nov. Published August 2020. Full-text: <https://doi.org/10.3201/eid2611.202736>

In the [Faroe Islands](#), an autonomous territory within the Kingdom of Denmark with a population of around 50,000, only 6 out of 1,075 randomly selected participants (0.6%) tested seropositive for antibodies to SARS-CoV-2 ([Petersen 2020](#)). At present, small islands tend to have low seropositivity rates.

UK

Ward H, Atchison C, Whitaker M, et al. **Antibody prevalence for SARS-CoV-2 following the peak of the pandemic in England: REACT2 study in 100,000 adults.** Imperial College London 2020. Pre-print: <https://www.imperial.ac.uk/media/imperial-college/institute-of-global-health-innovation/Ward-et-al-120820.pdf>

By the end of June 2020, an estimated 3.4 million people, or slightly under 6% of the UK population, had antibodies to the virus and had likely had COVID-19. London had the highest numbers (13%), while the South West had the lowest (3%) ([Ward 2020](#)). Black, Asian and minority ethnic (BAME) individuals were between two and three times as likely to have had SARS-CoV-2 infection compared to white people. An interesting trend: young people aged 18-24 had the highest rates (8%), while older adults aged 65 to 74 were least likely to have been infected (3%).

CHINA

Xu X, Sun J, Nie S, et al. **Seroprevalence of immunoglobulin M and G antibodies against SARS-CoV-2 in China.** Nat Med. 2020 Jun 5. PubMed: <https://pubmed.gov/32504052>. Full-text: <https://doi.org/10.1038/s41591-020-0949-6>

At the end of the 2020 winter epidemic, the seropositivity (IgM and IgG antibodies) in Wuhan was low, varying between 3.2% and 3.8% in different sub-cohorts ([Xu X 2020](#)).

SWITZERLAND

Stringhini S, Wisniak A, Piumatti G, et al. The Lancet, June 11, 2020. **Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study.** Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31304-0](https://doi.org/10.1016/S0140-6736(20)31304-0)

Geneva was a COVID-19 hot spot in Switzerland (5000 cases over < 2.5 months in half a million people). The seroprevalence increased from about 5% to about 11% over five

consecutive weekly sero-surveys among 2,766 randomly selected participants from a previous population-representative survey, and 1,339 household members aged 5 years and older (Stringhini 2020). Of note, young children (5–9 years) and older people (≥ 65 years) had significantly lower seroprevalence than the other age groups. Authors estimated that there were 11 infections for every COVID-19 confirmed case.

Hotspots of SARS-CoV-2 Transmission

HOSPITALS

Nagano T, Aarii J, Nishimura M, et al. **Diligent medical activities of a publicly designated medical institution for infectious diseases pave the way for overcoming COVID-19: A positive message to people working at the cutting edge.** Clin Infect Dis. 2020 May 31. PubMed: <https://pubmed.gov/32474577>. Full-text: <https://doi.org/10.1093/cid/ciaa694>

Standard preventive measures against infectious diseases can prevent SARS-CoV-2 exposure in medical staff. Of 509 medical staff members working to treat COVID-19 patients at the Hyogo Prefectural Kakogawa Medical Center, a large medical institution for infectious diseases in Japan (mean number of hospitalized COVID-19 patients was 20), none had IgG antibodies for SARS-CoV-2 on May 1–8 (Nagano 2020).

Callaghan AW, Chard AN, Arnold P, et al. **Screening for SARS-CoV-2 Infection Within a Psychiatric Hospital and Considerations for Limiting Transmission Within Residential Psychiatric Facilities - Wyoming, 2020.** MMWR Morb Mortal Wkly Rep. 2020 Jul 3;69(26):825–829. PubMed: <https://pubmed.gov/32614815>. Full-text: <https://doi.org/10.15585/mmwr.mm6926a4>

Implementing expanded admission screening and infection prevention and control procedures is effective even within a psychiatric ward (Callaghan 2020).

Rincón A, Moreso F, López-Herradón A. **The keys to control a coronavirus disease 2019 outbreak in a haemodialysis unit.** Clinical Kidney Journal, 13 July 2020. Full-text: <https://doi.org/10.1093/ckj/sfaa119>

In an hemodialysis unit in Barcelona, 18% of patients receiving treatment became infected (Rincón 2020). The main risk factors for SARS-CoV-2 infection were sharing health-care transportation, living in a nursing home and having been admitted to the reference hospital within the previous 2 weeks.

Vahidy FS, Bernard DW, Boom ML, et al. **Prevalence of SARS-CoV-2 Infection Among Asymptomatic Health Care Workers in the Greater Houston, Texas, Area.** JAMA Netw Open. 2020 Jul 1;3(7):e2016451. PubMed: <https://pubmed.gov/32716512>. Full-text: <https://doi.org/10.1001/jamanetworkopen.2020.16451>

Among clinical HCWs, 5.4% from COVID-19 units and 0.6% from non-COVID units had RT-PCR test results positive for SARS-CoV-2 (Vahidy 2020).

LONG-TERM CARE FACILITIES

Marossy A, Rakowicz S, Bhan A, et al. **A study of universal SARS-CoV-2 RNA testing of residents and staff in a large group of care homes in South London.** *J Infect Dis.* 2020 Sep 5:jiaa565. PubMed: <https://pubmed.gov/32889532>. Full-text: <https://doi.org/10.1093/infdis/jiaa565>

In one of the largest studies of care homes in Europe which involved 2,455 individuals, residents and staff from 37 care homes in the London Borough of Bromley were tested irrespective of symptoms. Overall, the point prevalence of SARS-CoV-2 infection was 6.5% with a higher rate in residents (9.0%) than in staff (4.7%) (Marossy 2020).

Fisman DN, Bogoch I, Lapointe-Shaw L, et al. **Risk Factors Associated With Mortality Among Residents With Coronavirus Disease 2019 (COVID-19) in Long-term Care Facilities in Ontario, Canada.** *JAMA*, published July 22, Full-text: <https://doi.org/10.1001/jamanetworkopen.2020.15957>

Hotspot LTCF. In a study from Ontario, Canada, the incidence of mortality was more than 13 times greater than that seen in community-living adults older than 69 years during a similar period (Fisman 2020).

Graham NSN, Junghans C, McLaren R, et al. **High rates of SARS-CoV-2 seropositivity in nursing home residents.** *J Infection* August 26, 2020a. Full-text: <https://doi.org/10.1016/j.jinf.2020.08.040>

Some nursing homes in the UK achieved fairly high seropositivity rates. In one study, 72% percent of nursing home residents were anti-SARS-CoV-2 IgG antibody positive (Graham 2020). Seropositivity was not associated with the presence of comorbidities.

ECDC Public Health Emergency Team, Danis K, Fonteneau L, et al. **High impact of COVID-19 in long-term care facilities, suggestion for monitoring in the EU/EEA.** May 2020. *Eurosurveillance*, Volume 25, Issue 22, 04/Jun/2020 Article. Full-text: <https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.22.2000956>

Residents in long-term care facilities contribute 30–60% of all COVID-19 deaths in many European countries (ECDC 2020). Surveillance and infection prevention and control measures are paramount: identify clusters early, decrease the spread within and between facilities and reduce the size and severity of outbreaks.

Graham N, Junghans C, Downes R, et al. **SARS-CoV-2 infection, clinical features and outcome of COVID-19 in United Kingdom nursing homes.** *J Infect* 2020b, Jun 3:S0163-4453(20)30348-0. PubMed: <https://pubmed.gov/32504743>. Full-text: <https://doi.org/10.1016/j.jinf.2020.05.073>

Hotspot nursing home. In one UK investigation involving 394 residents and 70 staff in 4 nursing homes in central London, 26% of residents died over a two-month period (Graham 2020). Systematic testing identified 40% of residents as positive for SARS-CoV-2 and of these, 43% were asymptomatic and 18% had only atypical symptoms during the two weeks prior to testing. Of note, this was also true of many residents in the days leading up to death indicating that even in severe COVID-19, fever and cough were commonly absent. 4% of asymptomatic staff also tested positive.

Dora AV, Winnett A, Jatt LP, et al. **Universal and Serial Laboratory Testing for SARS-CoV-2 at a Long-Term Care Skilled Nursing Facility for Veterans - Los Angeles, California, 2020.** MMWR Morb Mortal Wkly Rep. 2020 May 29;69(21):651-655. PubMed: <https://pubmed.gov/32463809>. Full-text: <https://doi.org/10.15585/mmwr.mm6921e1>

Again and again: Test them all, immediately. After an outbreak at a long-term care nursing facility, all residents, regardless of symptoms, underwent serial (approximately weekly) nasopharyngeal SARS-CoV-2 RT-PCR testing. Nineteen of 99 (19%) residents had positive test results for SARS-CoV-2 (Dora 2020). Fourteen of the 19 residents with COVID-19 were asymptomatic at the time of testing. Among these, eight developed symptoms 1-5 days after specimen collection and were later classified as presymptomatic.

LEISURE VENUES (BARS, CLUBS, CHOIRS, KARAOKE, DISCOS, ETC.)

NCOMG. The national COVID-19 outbreak monitoring group. **COVID-19 outbreaks in a transmission control scenario: challenges posed by social and leisure activities, and for workers in vulnerable conditions, Spain, early summer 2020.** Eurosurveillance Volume 25, Issue 35, 03/Sep/2020. Full-text: <https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.35.2001545>

Hotspot Movida. From mid-June to 2 August, excluding single household outbreaks, 673 outbreaks were notified in Spain (NCOMG 2020). There were two main settings where over 55% of active outbreaks (303/551) and over 60% (3,815/6,208) of active outbreak cases originated: First, social settings such as family gatherings or private parties (112 outbreaks, 854 cases), followed by those linked to leisure venues such as bars, restaurants, or clubs (34 outbreaks, over 1,230 cases). Second, occupational settings (representing 20% of all active outbreaks), mainly among workers in the fruit and vegetable sector (31 outbreaks and around 500 cases) and workers at slaughterhouses or meat processing plants (12 outbreaks and around 360 cases).

Data from Japan showed that of a total of 61 COVID-19 clusters, 18 (30%) were in healthcare facilities; 10 (16%) in care facilities of other types, such as nursing homes and day care centers; 10 (16%) in restaurants or bars; 8 (13%) in workplaces; 7 (11%) in music-related events, such as live music concerts, chorus group rehearsals, and kara-

ke parties; 5 (8%) in gymnasiums; 2 (3%) in ceremonial functions; and 1 (2%) in transportation-related incident in an airplane (Furuse 2020). Of note, 41% of probable primary case-patients were pre-symptomatic or asymptomatic at the time of transmission. 45% had cough. Many clusters were associated with heavy breathing in close proximity.

Kang CR, Lee JY, Park Y, Huh IS, Ham HJ, Han JK, et al. **Coronavirus disease exposure and spread from nightclubs, South Korea.** *Emerg Infect Dis.* 2020 Sep. Full-text: <https://doi.org/10.3201/eid2610.202573>

Superspreading events in nightclubs have the potential to spark local resurgence of cases. Large-scale testing (41,612 total tests!) for active case-finding among persons who visited 5 Itaewon nightclubs in downtown Seoul found positive results in 0.19% (67/35,827) of nightclub visitors, 0.88% (51/5,785) of their contacts, and 0.06% (1/1,627) of anonymously tested persons (Kang 2020). In total, 246 COVID-19 cases were associated with the reopening of nightclubs in Seoul.

Lewis M, Sanchez R, Auerbach S, et al. **COVID-19 Outbreak Among College Students After a Spring Break Trip to Mexico — Austin, Texas, March 26–April 5, 2020.** *MMWR Morb Mortal Wkly Rep.* ePub: 24 June 2020. Full-text: <http://dx.doi.org/10.15585/mmwr.mm6926e1>

Asymptomatic persons or those with mild symptoms likely played an important role in sustaining transmission. A college trip is an ideal environment for SARS-CoV-2 transmission (64 cases on one trip, 14 asymptomatic and 50 symptomatic; Lewis 2020).

WORKPLACES

Waltenburg MA, Victoroff T, Rose CE, et al. **Update: COVID-19 Among Workers in Meat and Poultry Processing Facilities – United States, April–May 2020.** *MMWR Morb Mortal Wkly Rep.* ePub: 7 July 2020. Full-text: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6927e2.htm>

Meat and poultry processing facilities are SARS-CoV-2 hotspots. One study reported 16,233 COVID-19 cases and 86 COVID-19–related deaths among workers in 239 facilities (Waltenburg 2020). The percentage of workers with COVID-19 ranged from 3.1% to 24.5% per facility.

Among seven facilities that implemented facility-wide testing, the crude prevalence of asymptomatic or presymptomatic infections among 5,572 workers who had positive SARS-CoV-2 test results was 14.4% (Waltenburg 2020).

Steinberg J, Kennedy ED, Basler C, et al. **COVID-19 Outbreak Among Employees at a Meat Processing Facility — South Dakota, March–April 2020.** *MMWR Morb Mortal Wkly Rep* 2020;69:1015–1019. Full-text: <http://dx.doi.org/10.15585/mmwr.mm6931a2>

Early outbreak in a meat processing facility in the US. From March 16 to April 25, 25.6% (929) of employees and 8.7% (210) of their contacts were diagnosed with COVID-19; two employees died (Steinberg 2020). The highest attack rates occurred among employees who worked < 6 feet (2 meters) from one another on the production line.

SCHOOLS

Davies NG, Klepac P, Liu Y et al. **Age-dependent effects in the transmission and control of COVID-19 epidemics.** Nat Med 2020, June 16. <https://doi.org/10.1038/s41591-020-0962-9>

Children have a lower susceptibility to infection. Using epidemic data from Canada, China, Italy, Japan, Singapore, and South Korea, one group found that susceptibility to infection in individuals under 20 years of age was approximately half that of adults aged over 20 years, and clinical symptoms manifest in 21% of infections in 10- to 19-year-olds, rising to 69% of infections in people aged over 70 years (Davis 2020).

Panovska-Griffiths J, Kerr CC, Stuart RM, et al. **Determining the optimal strategy for reopening schools, the impact of test and trace interventions, and the risk of occurrence of a second COVID-19 epidemic wave in the UK: a modelling study.** Lancet Child Adolesc Health 2020, August 03, 2020. Full-text: [https://doi.org/10.1016/S2352-4642\(20\)30250-9](https://doi.org/10.1016/S2352-4642(20)30250-9)

Reopening of schools must be accompanied by large-scale, population-wide testing of symptomatic individuals and effective tracing of their contacts, followed by isolation of diagnosed individuals. Without these levels of testing and contact tracing, reopening of schools together with gradual relaxing of the lockdown measures are likely to induce a second wave that would peak in December 2020 (Panovska-Griffiths).

Brown NE, Bryant-Genevier J, Bandy U, Browning CA, Berns AL, Dott M, et al. **Anti-body responses after classroom exposure to teacher with coronavirus disease, March 2020.** Emerg Infect Dis. 2020 Sep [date cited]. <https://doi.org/10.3201/eid2609.201802>

No big surprise: classroom interaction between an infected teacher and students might result in virus transmission. After returning from Europe to the United States on March 1, 2020, a symptomatic teacher received positive test results. In total 2/21 students exposed to the teacher in the classroom had positive serologic results.

Cheng SY, Wang J, Shen AC, et al. **How to Safely Reopen Colleges and Universities During COVID-19: Experiences From Taiwan.** Ann Int Med 2020, Jul 2. Full-text: <https://doi.org/10.7326/M20-2927>

Taiwan is one of the few countries where schools are functioning normally. To secure the safety of students and staff, the Ministry of Education in Taiwan established general guidelines, including a combination of strategies such as – our future? - active

campus-based screening and access control; school-based screening and quarantine protocols; student and faculty quarantine when warranted; mobilization of administrative and health center staff; regulation of dormitories and cafeterias; and reinforcement of personal hygiene, environmental sanitation, and indoor air ventilation practices (Cheng SY 2020). Depressing (un monde de con), but probably necessary.

Torres JP, Piñera C, De La Maza V, et al. **SARS-CoV-2 antibody prevalence in blood in a large school community subject to a Covid-19 outbreak: a cross-sectional study.** Clin Infect Dis. 2020 Jul 10:ciaa955. PubMed: <https://pubmed.gov/32649743>. Full-text: <https://doi.org/10.1093/cid/ciaa955>

School-based outbreak are common with cases among teachers, children and parents. In some situations, the index cases were teachers and/or parents (Torres 2020). Re-opening schools should focus on avoiding new cases among teachers

MASS GATHERINGS

Anonymous. **Deutsche Box-Olympiamannschaft mit Coronavirus infiziert.** Die Zeit 2020, published 12 September. Full-text: <https://www.zeit.de/sport/2020-09/trainingslager-oesterreich-deutsche-box-olympiamannschaft-coronavirus-infektion-quarantaene>

In an unintentional experiment, the German national team of amateur boxers has proved that you can achieve a 100% transmission rate in a small group within days. In a training camp, some of the 18 athletes and 7 coaches and supervisors had cold symptoms four days ago. Now all 25 persons have tested positive for SARS-CoV-2. So far, no serious cases.

Mubarak N, Zin CS. **Religious tourism and mass religious gatherings - The potential link in the spread of COVID-19. Current perspective and future implications.** Travel Med Infect Dis. 2020 Jun 9;36:101786. PubMed: <https://pubmed.gov/32531422>. Full-text: <https://doi.org/10.1016/j.tmaid.2020.101786>

Religious mass gatherings should probably postponed. Of particular concern are pilgrims returning to home countries with inadequate quarantine and diagnostic infrastructure, especially those over 50 years old or suffering from chronic disease such as diabetes or cardiovascular disease (Mubarak 2020).

Khan A, Bieh KL, El-Ganainy A, et al. **Estimating the COVID-19 Risk during the Hajj Pilgrimage.** Journal of Travel Medicine, 05 September 2020. Full-text: <https://doi.org/10.1093/jtm/taaa157>

A religious gathering that attracts 2.5 million pilgrims from over 150 countries has clearly the potential to create a giga-spreading event. Designated ward and ICU beds could be saturated within days. Reducing the number of pilgrims and excluding foreign pilgrims is a wise decision (Khan 2020)

Nayar KR, Koya SF, Ramakrishnan V, et al. **Call to avert acceleration of COVID-19 from India's Sabarimala pilgrimage of 25 million devotees.** Journal of Travel Medicine, 05 September 2020, taaa153. Full-text: <https://doi.org/10.1093/jtm/taaa153>

Hajj or the Sabarimala annual 41-day long Hindu pilgrimage attended by an average of 25 million pilgrims (Nayar 2020). How would proceed to require a negative SARS-CoV-2 antigen test from all pilgrims?

CLOSED AND DENSELY POPULATED SPACES

Njuguna H, Wallace M, Simonson S, et al. **Serial Laboratory Testing for SARS-CoV-2 Infection Among Incarcerated and Detained Persons in a Correctional and Detention Facility — Louisiana, April–May 2020.** MMWR Morb Mortal Wkly Rep. ePub: 29 June 2020. Full-text: <http://dx.doi.org/10.15585/mmwr.mm6926e2>

High COVID-19 attack rates in prisons. Among 98 incarcerated and detained persons in Louisiana who were quarantined because of virus exposure, 71 (72%) had lab-confirmed SARS-CoV-2 infection identified through serial testing, among them 45% without any symptoms at the time of testing (Njuguna 2020). Serial testing of contacts of persons with COVID-19 in correctional and detention facilities can identify asymptomatic and presymptomatic persons who would be missed through symptom screening alone.

Jiménez MC, Cowger TL, Simon LE, Behn M, Cassarino N, Bassett MT. **Epidemiology of COVID-19 Among Incarcerated Individuals and Staff in Massachusetts Jails and Prisons.** JAMA Netw Open 2020;3(8). Full-text: <https://doi.org/10.1001/jamanetworkopen.2020.18851>

In July 2020, the rate of COVID-19 among incarcerated individuals was nearly 3 times that of the Massachusetts general population and 5 times the US rate (Jiménez 2020). Of 14,987 individuals incarcerated across Massachusetts prison facilities, 1032 confirmed cases of COVID-19 were reported among incarcerated individuals (n = 664) and staff (n = 368).

Saloner B, Parish K, Ward JA. **COVID-19 Cases and Deaths in Federal and State Prisons.** JAMA July 8, 2020. Full-text: <https://doi.org/10.1001/jama.2020.12528>

By June 6, 2020, there had been 42,107 cases of COVID-19 and 510 deaths among 1.3 million prisoners in the US (Saloner 2020).

Maxmen A. **California's San Quentin prison declined free coronavirus tests and urgent advice — now it has a massive outbreak.** Nature NEWS 07 July 2020. Full-text: <https://doi.org/10.1038/d41586-020-02042-9>

In July 2020, more than one-third of the inmates and staff (1,600 people) in San Quentin Prison tested positive (Maxmen 2020). Six had died.

Rogers JH, Link AC, McCulloch D, et al. **Characteristics of COVID-19 in Homeless Shelters : A Community-Based Surveillance Study.** Ann Intern Med. 2020 Sep 15. PubMed: <https://pubmed.gov/32931328>. Full-text: <https://doi.org/10.7326/M20-3799>

In this cross-sectional, community-based surveillance study of 14 homeless shelters in King County, Washington, Helen Chu, Julia Rogers and colleagues divided the number of positive cases by the total number of participant encounters, regardless of symptoms. Among 1434 encounters, 29 (2%) cases of SARS-CoV-2 infection were detected across 5 shelters. **Eighty-six percent of persons with positive test results slept in a communal space rather than in a private or shared room (Rogers 2020).**

Payne DC, Smith-Jeffcoat SE, Nowak G, et al. **SARS-CoV-2 Infections and Serologic Responses from a Sample of U.S. Navy Service Members — USS Theodore Roosevelt, April 2020.** MMWR Morb Mortal Wkly Rep. ePub: 9 June 2020. Full-text: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6923e4.htm>

In late March 2020, a large outbreak on the aircraft carrier USS Theodore Roosevelt was characterized by widespread transmission with relatively mild symptoms and asymptomatic infection among mostly young, healthy adults with close, congregate exposures. One fifth of infected participants reported no symptoms. Preventive measures, such as using face-coverings and observing social distancing, reduced risk for infection: among 382 service members, those who reported taking preventive measures had a lower infection rate than did those who did not report taking these measures (e.g., wearing a face-covering, 56% versus 81%; avoiding common areas, 54% versus 68%; and observing social distancing, 55% versus 70%, respectively) (Payne 2020).

Special Aspects of the Pandemic

PREPAREDNESS

Pham QT, Rabaa MA, Duong HL, et al. **The first 100 days of SARS-CoV-2 control in Vietnam.** Clin Infect Dis 2020, published 1 August. Full-text: <https://doi.org/10.1093/cid/ciaa1130>

Vietnam did remarkably well. One hundred days after the first SARS-CoV-2 case was reported in Vietnam on January 23rd, 270 cases were confirmed, with no deaths. Although there was a high proportion of asymptomatic and imported cases as well as evidence for substantial pre-symptomatic transmission, Vietnam controlled SARS-CoV-2 spread through the early introduction of mass communication, meticulous contact-tracing with strict quarantine, and international travel restrictions (Pham QT 2020). A lesson for the world?

Looi MK. **Covid-19: Japan ends state of emergency but warns of "new normal"**. BMJ. 2020 May 26;369:m2100. PubMed: <https://pubmed.gov/32457055>. Full-text: <https://doi.org/10.1136/bmj.m2100>

Japan has done a good job. Public adherence to the rules, along with cluster tracing and a ban on mass gatherings, seems to have achieved success in bringing the outbreak under control,

If, as in Japan, widespread mask use and hygiene is a normal part of etiquette, combating SARS-CoV-2 is easier (Looi 2020).

Stoke EK, Zambrano LD, Anderson KN. **Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020**. MMWR June 15, 2020. Full-text: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm>

In June, the CDC reported data on 1,320,488 laboratory-confirmed COVID-19 cases. Overall, 184,673 (14%) patients were hospitalized, 29,837 (2%) were admitted to an intensive care unit (ICU), and 71,116 (5%) died. Hospitalizations were six times higher among patients with a reported underlying condition (45.4%) than those without reported underlying conditions (7.6%). Deaths were 12 times higher among patients with reported underlying conditions (19.5%) compared with those without reported underlying conditions (1.6%) (Stoke 2020).

UNWILLINGNESS TO PREPARE/DENIAL (UK, USA, BRAZIL)

NEJM Editors. **Dying in a Leadership Vacuum**. N Engl J Med 2020; 383:1479-1480. Full-text: <https://www.nejm.org/doi/full/10.1056/NEJMe2029812>

SARS-CoV-2 and the COVID-19 pandemic became a test of leadership. With no good options to combat a novel pathogen, countries were forced to make hard choices about how to respond. In the United States, the leaders have failed that test.

Yehya N, Venkataramani A, Harhay MO. **Statewide Interventions and Covid-19 Mortality in the United States: An Observational Study**. Clin Infect Dis. 2020 Jul 8. PubMed: <https://pubmed.gov/32634828>. Full-text: <https://doi.org/10.1093/cid/ciaa923>

Every day counts. In this large, nationwide study, later statewide emergency declarations and school closures were associated with higher COVID-19 mortality. Each day of delay increased mortality risk by 5 to 6% (Yehya 2020).

Maxmen A. **Why the United States is having a coronavirus data crisis**. Nature 2020, published 25 August. Full-text: <https://www.nature.com/articles/d41586-020-02478-z>

To respond to a pandemic, you need reliable information on who is infected, why and where. Unfortunately, many countries suffered from a dearth of data (Maxmen 2020).

SPLENDID ISOLATION (NEW ZEALAND, AUSTRALIA)

Baker MG, Anglemyer A. **Successful Elimination of Covid-19 Transmission in New Zealand.** N Engl J Med 2020, published 7 August. Full-text: <https://www.nejm.org/doi/full/10.1056/NEJMc2025203>

Heywood AE, Macintyre CR. **Elimination of COVID-19: what would it look like and is it possible?** Lancet 2020, published 6 August. Full-text: [https://doi.org/10.1016/S1473-3099\(20\)30633-2](https://doi.org/10.1016/S1473-3099(20)30633-2)

Is elimination of SARS-CoV-2 possible (Hewyood 2020)? Geographical isolated islands or island states should be the identical candidates for elimination trials. However, even New Zealand which viewed itself in the post-elimination stage and where public life had returned to near normal (Baker 2020), was suddenly called back into COVID-19 reality when new cases were discovered in early August. The elimination of any infectious disease is ambitious, requiring substantial resources. They suggest a zero-case scenario of not less than three months before declaring an area SARS-CoV-2-free. For obvious reasons, islands or island states have the best chances to achieve this goal (Hewyood 2020).

Seemann T, Lance CR, Sherry NL, et al. **Tracking the COVID-19 pandemic in Australia using genomics.** Nat Commun 11, 4376 (2020). Full-text: <https://doi.org/10.1038/s41467-020-18314-x>

Multiple SARS-CoV-2 importations by returned international travelers drove transmission in Australia, with travel-related cases responsible for establishing ongoing transmission lineages (each with 3–9 cases) accounting for over half of locally acquired cases (Seemann 2020).

THE UNKNOWN (?) OUTCOME

Kalk A, Schultz A. **SARS-CoV-2 epidemic in African countries—are we losing perspective?** Lancet, August 07, 2020. Full-text: [https://doi.org/10.1016/S1473-3099\(20\)30563-6](https://doi.org/10.1016/S1473-3099(20)30563-6)

Lockdown for everybody? Maybe not. In the Democratic Republic of the Congo and Malawi, for instance, only 2-3% of the population is older than 65 years. Under these circumstances, full lockdown measures might cause more harm than SARS-CoV-2 itself (Kalk 2020).

Twahirwa Rwema JO, Diouf D, Phaswana-Mafuya N, et al. **COVID-19 Across Africa: Epidemiologic Heterogeneity and Necessity of Contextually Relevant Transmission Models and Intervention Strategies.** Ann Intern Med. 2020 Jun 18. PubMed: <https://pubmed.gov/32551812>. Full-text: <https://doi.org/10.7326/M20-2628>

Europe without Russia has a surface of roughly 6 million km², Africa has 30 million km². That should explain by itself that the burden and outcomes associated with COVID-19 in Africa shows substantial variations across African countries (Twahirwa 2020).

Walker PG, Whittaker C, Watson OJ, et al. **The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries.** Science 12 Jun 2020. Full-text: <https://DOI.ORG/10.1126/science.abc0035>

The impact of the SARS-CoV-2 pandemic in low- and middle-income countries (LMIC) is still unknown. On one hand, we have an overall younger population, on the other hand, there is a higher burden of infectious diseases such as AIDS and TB already, and of poverty-related determinants of poorer health outcomes such as malnutrition (Walker 2020). There is also a more persistent spread to older age categories (higher levels of household-based transmissions) and poorer quality health care and lack of health care capacity.

The SARS-CoV-2 pandemic: Past and Future

NATURAL COURSE OF A PANDEMIC

Barbarossa MV, Fuhrmann J, Meinke JH, et al. **Modeling the spread of COVID-19 in Germany: Early assessment and possible scenarios.** PLoS One. 2020 Sep 4;15(9):e0238559. PubMed: <https://pubmed.gov/32886696>. Full-text: <https://doi.org/10.1371/journal.pone.0238559>

Without restrictive measures, about 32 million total infections and 730,000 deaths could result in Germany alone over the course of the epidemic (Barbarossa 2020).

THE 2020 LOCKDOWNS

Sudharsanan N, Didzun O, Bärnighausen T, Geldsetzer P. **The Contribution of the Age Distribution of Cases to COVID-19 Case Fatality Across Countries - A 9-Country Demographic Study.** Ann Intern Med 2020, published 22 July. Full-text: <https://doi.org/10.7326/M20-2973>

The overall observed case-fatality rates (CFR) vary widely, with the highest rates in Italy (9.3%) and the Netherlands (7.4%) and the lowest rates in South Korea (1.6%) and Germany (0.7%). This cross-sectional study of population-based data from China, France, Germany, Italy, the Netherlands, South Korea, Spain, Switzerland, and the US finds that age distribution of cases explains 66% of the variation of across countries, with a resulting age-standardized median CFR of 1.9%. See also the editorial by David N. Fisman, Amy L. Greer, and Ashleigh R. Tuite: **Age Is Just a Number: A Critically Important Number for COVID-19 Case Fatality;** full-text: <https://doi.org/10.7326/M20-4048>.

David N. Fisman, Amy L. Greer, and Ashleigh R. Tuite: **Age Is Just a Number: A Critically Important Number for COVID-19 Case Fatality;** full-text: <https://doi.org/10.7326/M20-4048>.

During the first European wave of the SARS-CoV-2 pandemic, case-fatality rates (CFR) varied widely, with the highest rates in Italy (9.3%) and the Netherlands (7.4%) and the lowest rates in South Korea (1.6%) and Germany (0.7%) (Sudharsanan 2020, Fisman 2020). The study also found that age distribution of cases explains 66% of the variation of across countries.

Kissler SM, Kishore N, Prabhu M, et al. **Reductions in commuting mobility correlate with geographic differences in SARS-CoV-2 prevalence in New York City.** Nat Commun. 2020 Sep 16;11(1):4674. PubMed: <https://pubmed.gov/32938924>. Full-text: <https://doi.org/10.1038/s41467-020-18271-5>

SARS-CoV-2 prevalence varied substantially between New York City boroughs between 22 March and 3 May 2020 (for example, Manhattan: 11.3%; South Queens: 26.0%). These differences in prevalence correlate with antecedent reductions in commuting-style mobility between the boroughs. Prevalence was lowest in boroughs with the greatest reductions in morning movements out of and evening movements into the borough (Kissler 2020).

Czeisler MÉ, Tynan MA, Howard ME, et al. **Public Attitudes, Behaviors, and Beliefs Related to COVID-19, Stay-at-Home Orders, Nonessential Business Closures, and Public Health Guidance - United States, New York City, and Los Angeles, May 5-12, 2020.** MMWR Morb Mortal Wkly Rep. 2020 Jun 19;69(24):751-758. PubMed: <https://pubmed.gov/32555138>. Full-text: <https://doi.org/10.15585/mmwr.mm6924e1>

Most people agreed: during the week of May 5-12, 2020, a survey among 2,402 adults in New York City and Los Angeles and broadly across the United States found widespread support of stay-at-home orders and nonessential business closures and high degree of adherence to COVID-19 mitigation guidelines (Czeisler 2020). 74-82% reported they would not feel safe if these restrictions were lifted nationwide at the time the survey was conducted. In addition, among those who reported that they would not feel safe, some indicated that they would nonetheless want community mitigation strategies lifted and would accept associated risks (13-17%, respectively).

Moreland A, Herlihy C, Tynan MA, et al. **Timing of State and Territorial COVID-19 Stay-at-Home Orders and Changes in Population Movement - United States, March 1-May 31, 2020.** MMWR Morb Mortal Wkly Rep. 2020 Sep 4;69(35):1198-1203. PubMed: <https://pubmed.gov/32881851> . Full-text: <https://doi.org/10.15585/mmwr.mm6935a2>

US Americans were compliant to mandatory stay-at-home orders. Based on location data from mobile devices, in 97.6% of counties these orders were associated with decreased median population movement (Moreland 2020).

Flaxman S, Mishra S, Gandy A, et al. **Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe.** Nature. 6/2020 Jun 8. PubMed: <https://pubmed.gov/32512579>. Full-text: <https://doi.org/10.1038/s41586-020-2405-7>

According to one study, between 12 and 15 million individuals in Europe had been infected with SARS-CoV-2 by May 4th, representing between 3.2% and 4.0% of the population (Flaxman 2020). Percentages of total population infected were for Austria 0.76% (0.59% - 0.98%), Belgium 8.0 % (6.1% - 11%), Denmark 1.0% (0.81% - 1.4%), France 3.4% (2.7% - 4.3%), Germany 0.85% (0.66% - 1.1%), Italy 4.6% (3.6% - 5.8%), Norway 0.46% (0.34% - 0.61%), Spain 5.5% (4.4% - 7.0%), Sweden 3.7% (2.8% - 5.1%), Switzerland 1.9% (1.5% - 2.4%) and United Kingdom 5.1% (4.0% - 6.5%).

Habib H. **Has Sweden's controversial covid-19 strategy been successful?** BMJ. 2020 Jun 12;369:m2376. PubMed: <https://pubmed.gov/32532807>. Full-text: <https://doi.org/10.1136/bmj.m2376>

Has Sweden's controversial covid-19 strategy been successful? After a negative press at the beginning of the 2020 summer (Habib 2020) which stressed that the country was still far away from herd immunity and the death toll 5 to 10 times higher than in neighboring Denmark and Finland, the evaluation in October has changed...

FIRST AUTUMN, FIRST WINTER

Verdery AM, Smith-Greenaway E, Margolis R, Daw J. **Tracking the reach of COVID-19 kin loss with a bereavement multiplier applied to the United States.** Proc Natl Acad Sci U S A. 2020 Jul 10;202007476. PubMed: <https://pubmed.gov/32651279>. Full-text: <https://doi.org/10.1073/pnas.2007476117>

In the US, every death from COVID-19 will leave approximately nine bereaved, i.e., people who lost a grandparent, parent, sibling, spouse, or child (Verdery 2020).

MEASURING THE EPIDEMIC

Westhaus S, Weber FA, Schiwy S, et al. **Detection of SARS-CoV-2 in raw and treated wastewater in Germany - Suitability for COVID-19 surveillance and potential transmission risks.** Sci Total Environ 2020 August 18;751:141750. PubMed: <https://pubmed.gov/32861187>. Full-text: <https://doi.org/10.1016/j.scitotenv.2020.141750>

SARS-CoV-2 can be detected in wastewater in Germany using RT-qPCR. The total load of gene equivalents in wastewater correlated with the cumulative and the acute number of COVID-19 cases reported in the respective catchment areas. Thus, wastewater-based epidemiology can be regarded as a complementary measure to survey the outbreak (Westhaus 2020). (Important note: wastewater is no route for SARS-CoV-2 transmission to humans! All replication tests were negative tests for replication.)

Thomas LJ, Hunag O, Yin F, et al. **Spatial heterogeneity can lead to substantial local variations in COVID-19 timing and severity.** PNAS September 10, 2020. Full-text: <https://doi.org/10.1073/pnas.2011656117>

Relaxation of mitigation measures leading to a resumption of “normal” diffusion may initially appear to have few negative effects, only to lead to deadly outbreaks weeks or months later (Thomas 2020). Public health messaging may need to stress that apparent lulls in disease progress are not necessarily indicators that the threat has subsided, and that areas “passed over” by past outbreaks could be impacted at any time.

HERD IMMUNITY: NOT YET

Brett TS, Rohani P. **Transmission dynamics reveal the impracticality of COVID-19 herd immunity strategies.** Proc Natl Acad Sci U S A. 2020 Sep 22:202008087. PubMed: <https://pubmed.gov/32963094>. Full-text: <https://doi.org/10.1073/pnas.2008087117>

Achieving herd immunity without overwhelming hospital capacity leaves little room for error, as the author of one paper put it (Brett 2020). In other words: their modeling did not support achieving herd immunity as a practical objective, requiring an unlikely balancing of multiple poorly defined forces.

Eckerle I, Meyer B. **SARS-CoV-2 seroprevalence in COVID-19 hotspots.** The Lancet July 06, 2020. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31482-3](https://doi.org/10.1016/S0140-6736(20)31482-3)

Comment on these findings. Most of the population appears to have remained unexposed to SARS-CoV-2, even in areas with widespread virus circulation. Any proposed approach to achieve herd immunity through natural infection is not only highly unethical, but also unachievable (Eckerle 2020). With a large majority of the population being infection-naïve, virus circulation can quickly return to early pandemic dimensions in a second wave once measures are lifted.

Buss LF, Prete Jr CA, Abraham CMM, et al. **COVID-19 herd immunity in the Brazilian Amazon.** medRxiv 2020, posted 21 September. Full-text: <https://doi.org/10.1101/2020.09.16.20194787>

As much as 66% of the population of Manaus (two million people), Brazil, could have been infected with SARS-CoV-2. Ester Sabino, Lewis Buss and colleagues show that the transmission of SARS-CoV-2 in Manaus increased quickly during March and April and declined more slowly from May to September. In June, one month following the epidemic peak, 44% of the population was seropositive for SARS-CoV-2. After correcting for confounding factors, the authors estimate the epidemic size to be 66% by early August 2020. Note that these findings have not yet been peer reviewed and that the results have recently been questioned.

Remember: herd immunity is defined as the proportion of a population that must be immune to an infectious disease, either by natural infection or vaccination, such that

new cases decline and R_0 falls below 1 (see also <https://www.nature.com/articles/d41586-020-02009-w>).

“VARIATION” – FINDING OF THE YEAR?

Bielecki M, Züst R, Siegrist D, et al. **Social distancing alters the clinical course of COVID-19 in young adults: A comparative cohort study.** Clin Inf Dis, June 29, 2020. Full-text: <https://doi.org/10.1093/cid/ciaa889>

Important finding that was long suspected: viral inoculum during infection or mode of transmission may be key factors determining the clinical course of COVID-19. The authors prospectively studied an outbreak in Switzerland among a population of 508 predominantly male soldiers with a median age of 21 years. Infections were followed in two spatially separated cohorts with almost identical baseline characteristics - before and after implementation of stringent social distancing. Results: of 354 soldiers infected prior to the implementation of social distancing, 30% fell ill. In contrast, none out of 154 soldiers in which infections (confirmed by NP swabs or serology) appeared after implementation of social distancing developed COVID-19.

PROTECTING PEOPLE AT RISK

Nguyen LH, Drew DA, Graham MS, et al. **Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study.** Lancet Public Health. 2020 Sep;5(9):e475-e483. PubMed: <https://pubmed.gov/32745512>. Full-text: [https://doi.org/10.1016/S2468-2667\(20\)30164-X](https://doi.org/10.1016/S2468-2667(20)30164-X)

Front-line health care workers are at increased risk of SARS-CoV-2 infection. In a prospective, observational cohort study in the UK and the USA, front-line health care workers were at increased risk for reporting a positive COVID-19 test (adjusted HR 11.6) (Nguyen 2020). An increased risk (HR 3.4) was even found after accounting for differences in testing frequency between front-line health care workers and the general community. Post-hoc analyses showed that Black, Asian, and minority ethnic health care workers are at especially high risk of SARS-CoV-2 infection, with at least a fivefold (!) increased risk of COVID-19 compared with the non-Hispanic white general community.

Emeruwa UN, Ona S, Shaman JL, et al. **Associations Between Built Environment, Neighborhood Socioeconomic Status, and SARS-CoV-2 Infection Among Pregnant Women in New York City.** JAMA 2020, June 18, 2020. Full-text: <https://doi.org/10.1001/jama.2020.11370>

In a cross-sectional study of 396 pregnant New York City residents, large household membership, household crowding, and low socioeconomic status were associated with a 2-3 fold higher risk of infection (Emeruwa 2020).

Hatcher SM, Agnew-Brune C, Anderson M, et al. **COVID-19 Among American Indian and Alaska Native Persons — 23 States, January 31–July 3, 2020.** MMWR Morb Mortal Wkly Rep 2020, published 19 August 2020. Full-text: <http://dx.doi.org/10.15585/mmwr.mm6934e1>

American Indian and Alaska Native (AI/AN) persons appear to be disproportionately affected by the COVID-19 pandemic. In one study, the overall COVID-19 incidence among AI/AN persons was 3.5 times that among white persons (594 per 100,000 AI/AN population compared with 169 per 100,000 white population) (Hatcher 2020).

Grasso D, Zafra M, Ferrero B, et al. **Covid de ricos, covid de pobres: las restricciones de la segunda ola exponen las desigualdades de Madrid.** El País 2020, published 17 September. Full-text: <https://elpais.com/espana/madrid/2020-09-16/covid-de-ricos-covid-de-pobres-las-restricciones-de-la-segunda-ola-exponen-las-desigualdades-de-madrid.html>

The authors explain that the number of infections is higher in the most vulnerable areas, where possible limitations will weigh the most.

PREVENTION: TESTING, TRACING, ISOLATING

Lash RR, Donovan CV, Fleischauer AT, et al. **COVID-19 Contact Tracing in Two Counties - North Carolina, June-July 2020.** MMWR Morb Mortal Wkly Rep. 2020 Sep 25;69(38):1360-1363. PubMed: <https://pubmed.gov/32970654>. Full-text: <https://doi.org/10.15585/mmwr.mm6938e3>

Despite aggressive efforts by health departments, many COVID-19 patients do not report contacts, and many contacts cannot be reached (Lash 2020). Staff members in North Carolina/US have investigated 5,514 (77%) persons with COVID-19 in Mecklenburg County and 584 (99%) in Randolph Counties: during periods of high COVID-19 incidence, 48% and 35% of patients reported no contacts, and 25% and 48 % of contacts were not reached. Median interval from index patient specimen collection to contact notification was 6 days. Improved timeliness of contact tracing, community engagement, and community-wide mitigation are needed to reduce SARS-CoV-2 transmission.

Clapham H, Hay J, Routledge I, et al. **Seroepidemiologic Study Designs for Determining SARS-COV-2 Transmission and Immunity.** Emerg Infect Dis. 2020 Jun 16;26(9). PubMed: <https://pubmed.gov/32544053>. Full-text: <https://doi.org/10.3201/eid2609.201840>

Test, test, test... but how accurate are the tests? Numerous challenges exist in terms of sample collection, what the presence of antibodies actually means, and appropriate analysis and interpretation to account for test accuracy and sampling biases (Clapham 2020). The authors review strengths and limitations of different assay types and study designs

Liang LL, Tseng CH, Ho HJ, Wu CY. **Covid-19 mortality is negatively associated with test number and government effectiveness.** Sci Rep. 2020 Jul 24;10(1):12567. Pub-Med: <https://pubmed.gov/32709854>. Full-text: <https://doi.org/10.1038/s41598-020-68862-x>

In a worldwide cross-sectional study (Liang LL 2020), the authors find that COVID-19 mortality is

- Negatively associated with
 - Test number per 100 people
 - Government effectiveness score
 - Number of hospital beds
- Positively associated with
 - Proportion of population aged 65 or older
 - Transport infrastructure quality score

Remember: Government effectiveness!

Jingwen Li, Chengbi Wu, Xing Zhang, Lan Chen, Xinyi Wang, Xiuli Guan, Jinghong Li, Zhicheng Lin, Nian Xiong. **Post-pandemic testing of SARS-CoV-2 in Huanan Seafood Market area in Wuhan, China.** Clinical Infectious Diseases 2020, published 25 July 2020. Full-text: <https://doi.org/10.1093/cid/ciaa1043>

Citywide mass nucleic acid testing of SARS-CoV-2 for all citizens is possible as shown in Wuhan city (14 May to 1 June 2020). The results are sometimes meager, revealing just 6 persons who test positive for SARS-CoV-2 (0.006% of 107,662 residents around the Huanan Seafood Market), but are able to suffocate a nascent epidemic (Jingwen L 2020).

Perkins TA, Cavany SM, Moore SM, et al. **Estimating unobserved SARS-CoV-2 infections in the United States.** PNAS August 21, 2020. Full-text: <https://doi.org/10.1073/pnas.2005476117>

Testing was a major limiting factor in assessing the extent of SARS-CoV-2 transmission during its initial invasion into the US (Perkins 2020). After a national emergency was declared, fewer than 10% of locally acquired, symptomatic infections in the US may were detected over a period of a month. This gap in surveillance during a critical phase of the epidemic resulted in a large, unobserved reservoir by early March.

CURFEWS

Andronico A, Kiem CT, Paireaux J, et al. **Evaluating the impact of curfews and other measures on SARS-CoV-2 transmission in French Guiana.** medRxiv 2020, posted 12 October. Full-text: <https://doi.org/10.1101/2020.10.07.20208314>

Might curfews be a less costly alternative, both economically and socially? In [French Guiana](#), an overseas département, a combination of curfews and targeted lockdowns in June and July 2020 was sufficient to avoid saturation of hospitals. On weekdays, residents were first ordered to stay at home 11 p.m., then at 9 p.m., later again at 7 p.m., and finally at 5 p.m. On weekends, everyone had to stay at home from 1 p.m. on Saturday ([Andronico 2020](#)). Whether curfews can be successfully adapted to other areas than French Guiana, is not known. French Guiana is a young territory with a median age is 25 years and the risk of hospitalisation following infection was only 30% that of France. About 20% of the population had been infected with SARS-CoV- by July 2020 ([Andronico 2020](#)). Be prepared though to see some curfews orders over the coming six months.

Outlook

Horton R. **Offline: The second wave.** Lancet 2020, June 27, 395, ISSUE 10242, P1960. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31451-3](https://doi.org/10.1016/S0140-6736(20)31451-3)

In June, scientists predicted a second SARS-CoV-2 wave in Europe. They were right. We should now hope that the current epidemic doesn't follow the scenario of the 1918 influenza pandemic ([Horton 2020](#)).

Petersen E, Koopmans M, Go U, et al. **Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics.** Lancet Inf Dis 2020, July 03, 2020. Full-text: [https://doi.org/10.1016/S1473-3099\(20\)30484-9](https://doi.org/10.1016/S1473-3099(20)30484-9)

How long will a combination of physical distancing, enhanced testing, quarantine, and contact tracing be needed? Historical evidence from prior influenza pandemics indicates that pandemics tend to come in waves over the first 2-5 years as population immunity builds-up (naturally or through vaccination) and that this is the most likely trajectory for SARS-CoV-2 ([Petersen 2020](#)).

Watsa M. **Rigorous wildlife disease surveillance.** Science 10 Jul 2020, 369: 145-147. Full-text: <https://doi.org/10.1126/science.abc0017>

Emerging infectious diseases (EID) associated with the wildlife trade remain the largest unmet challenge of current disease surveillance efforts. International or national conventions on pathogen screening associated with animals, animal products or their movements are urgently needed ([Watsa 2020](#)). Internationally recognized standard for managing wildlife trade on the basis of known disease risks should be established.

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2. Transmission

Bernd Sebastian Kamps

Christian Hoffmann

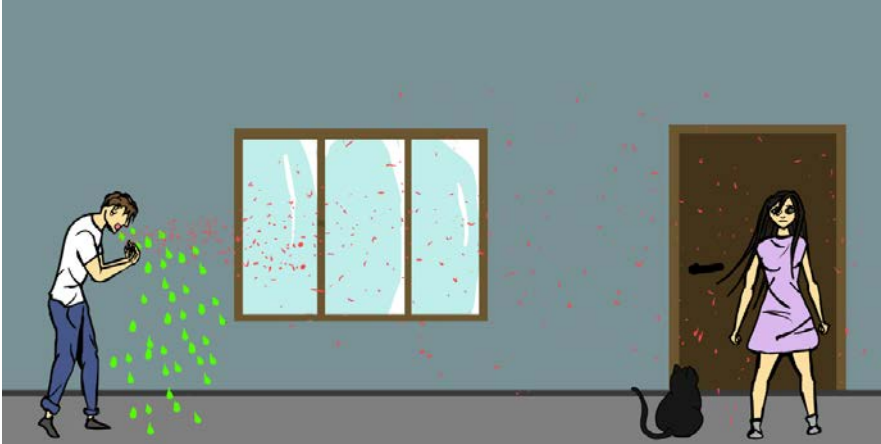


Figure 1. Transmission of SARS-CoV-2. 1) After coughing, sneezing, shouting and even after speaking – particularly loud speaking –, large droplets (green) drop to the ground around the young man. 2) In addition, some droplets, small and lightweight enough (red), are transported by air currents over longer distances (WHO 20200709). The second – aerosol – transmission is now recognized as a possibly relevant transmission route in the SARS-CoV-2. Adapted from Morawska 2020. Art work: Félix Prudhomme – IYENSS.

Introduction

Viruses have substantially influenced human health, interactions with the ecosphere, and societal history and structures (Chappell 2019). In a highly connected world, microbial evolution is boosted and pathogens exploit human behaviors to their own benefit (Morens 2013). This was critically shown during the SARS epidemic in 2003 (Kamps-Hoffmann 2003), the outbreak of Middle East Respiratory Syndrome coronavirus (MERS-CoV) (Zaki 2012), the last great Ebola epidemic in West Africa (Arwady 2015, Heymann 2015) and the Zika epidemic in 2015-2017 (Fauci 2016). Over the same time period, more virulent strains of known respiratory pathogens – H5N1 influenza virus, tuberculosis, avian H7N9 influenza virus – have emerged (Kamps-Hoffmann 2006, Jassal 2009, Gao 2013).

The Virus

SARS-CoV-2, Severe Acute Respiratory Syndrome coronavirus 2, is a highly transmissible ‘complex killer’ (Cyranoski 2020) that forced half of humanity, 4 billion people, to bunker down in their homes in the early spring of 2020. The respiratory disease rapidly evolved into a pandemic (Google 2020). In most cases, the illness is asymptomatic or paucisymptomatic and self-limited. A subset of infected individuals has severe symptoms and sometimes prolonged courses (Garner 2020). Around 10% of infected people need hospitalization and around one third of them treatment in intensive care units. The overall mortality rate of SARS-CoV-2 infection seems to be less than 1%.

Coronaviruses are tiny spheres of about 70 to 80 nanometers (a millionth of a millimeter) on thin-section electron microscopy (Perlman 2019). Compared to the size of a human, SARS-CoV-2 is as small as a big chicken compared to the planet Earth (El País). The *raison d’être* of SARS-CoV-2 is to proliferate, like that of other species, for example *H. sapiens sapiens* who has been successful in populating almost every corner of the world, sometimes at the expense of other species. SARS-CoV-2, for now, seems to be on a similarly successful track. By 7 June, only a handful of countries can claim to have been spared by the pandemic.

SARS-CoV-2’s global success has multiple reasons. The new coronavirus hijacks the human respiratory system to pass from one individual to another when people sneeze, cough, shout and speak. It is at ease both in cold and in warm climates; and, most importantly and unlike the two other deadly coronaviruses SARS-CoV and MERS-CoV, it manages to get transmitted to the next individual before it develops symptoms in the first one (see below, Asymptomatic Infection, page 104). There is no doubt that SARS-CoV-2 has a bright future – at least until the scientific community develops a safe vaccine (see the chapter *Vaccines*, page 199) and efficient drugs.

SARS-CoV-2 and its kin

SARS-CoV-2 is a **coronavirus** like

- SARS-CoV (cousin from the 2002/2003 epidemic),
- MERS-CoV (Middle East Respiratory Syndrome coronavirus),
- and a group of so-called CAR coronaviruses (for Community-Acquired Respiratory CoVs: 229E, OC43, NL63, HKU1).

The CAR group of viruses are highly transmissible and produce about 15 to 30% of common colds, typically in the winter months. On the contrary, SARS-CoV and MERS-CoV have case fatality rates of 10% and 34%, respectively, but

they never achieved pandemic spread. SARS-CoV-2, from a strictly viral point of view, is the shooting star in the coronavirus family: it combines high transmissibility with high morbidity and mortality.

SARS-CoV-2 is a **virus** like other commonly known viruses that cause human disease such as hepatitis C, hepatitis B, Ebola, influenza and human immunodeficiency viruses. (Note that the differences between them are bigger than those between humans and amebas.) With the exception of influenza, these viruses have a harder time infecting humans than SARS-CoV-2. **Hepatitis C virus (HCV)**, a major cause of chronic and often fatal liver disease, is mainly transmitted by percutaneous exposure to blood, by unsafe medical practices and, less frequently, sexually. The **human immunodeficiency virus (HIV)**, in addition to exposure to blood and perinatal transmission, also exploits sexual contact as a potent transmission route. **Hepatitis B virus (HBV)** is an even more versatile spreader than HCV and HIV as it can be found in high titers in blood, cervical secretions, semen, saliva, and tears; even tiny amounts of blood or contaminated secretions can transmit the virus. Ideal infection environments for HBV include, for example, schools, institutions and hospitals where individuals are in close and prolonged contact.

Of note, apart from HIV and hepatitis B and C, most viral diseases have no treatment. For example, there is no treatment for measles, polio, or smallpox. For influenza, decades of research have produced two specific drugs which have not been able to demonstrate reduced mortality – despite tests on thousands of patients. After 35 years of research, there is still no vaccine to prevent HIV infection.

Ecology of SARS-CoV-2

SARS-CoV-2 is present at high concentrations in the upper and lower respiratory tract (Zhu N 2020, Wang 2020, Huang 2020). The virus has also been found, albeit at low levels, in the kidney, liver, heart, brain, and blood (Puelles 2020). Outside the human body, the virus is more stable at low temperature and low humidity conditions, whereas warmer temperatures and higher humidity shorten the half-life (Matson 2020). It has also been shown to be detectable as an aerosol (in the air) for up to three hours, up to 24 hours on cardboard and up to two to three days on plastic and stainless steel (van Doremalen 2020). As expected, viral RNA was more likely to be found in areas immediately occupied by COVID-19 patients than in other hospital areas (Zhou J 2020). Another study documented contamination of toilets (toilet bowl, sink, and door handle) and air outlet fans (Ong SWX 2020). This is in line with the experience from MERS where many environmental surfaces of

patients' rooms, including points frequently touched by patients or healthcare workers, were contaminated by MERS-CoV (Bin 2016).

Person-to-person transmission

Person-to-person transmission of SARS-CoV-2 was established within weeks of identification of the first cases (Chan JF 2020, Rothe 2020). Shortly after, it was suggested that asymptomatic individuals would probably account for a substantial proportion of all SARS-CoV-2 transmissions (Nishiura 2020, Li 2020). Viral load can be high 2-3 days before the onset of symptoms and almost half of all secondary infections are supposed to be caused by pre-symptomatic patients (He 2020).

A key factor in the transmissibility of SARS-CoV-2 is the high level of viral shedding in the upper respiratory tract (Wolfel 2020), even among paucisymptomatic patients. Pharyngeal virus shedding is very high during the first week of symptoms, with a peak at $> 7 \times 10^8$ RNA copies per throat swab on day 4. Infectious virus was readily isolated from samples derived from the throat or lung. That distinguishes it from SARS-CoV, where replication occurred mainly in the lower respiratory tract (Gandhi 2020); SARS-CoV and MERS-CoV infect intrapulmonary epithelial cells more than cells of the upper airways (Cheng PK 2004, Hui 2018).

The shedding of viral RNA from sputum appears to outlast the end of symptoms and seroconversion is not always followed by a rapid decline in viral load (Wolfel 2020). This contrasts with influenza where persons with asymptomatic disease generally have lower quantitative viral loads in secretions from the upper respiratory tract than from the lower respiratory tract and a shorter duration of viral shedding than persons with symptoms (Ip 2017).

A recently published review summarized the evidence of human SARS-CoV-2 transmission (Meyerowitz 2020). Their key points:

1. Respiratory transmission is the dominant mode of transmission.
2. Vertical transmission occurs rarely; transplacental transmission has been documented.
3. Direct contact and fomite transmission are presumed but are likely only an unusual mode of transmission.
4. Although live virus has been isolated from saliva and stool and viral RNA has been isolated from semen and blood donations, there are no reported cases of SARS-CoV-2 transmission via fecal-oral, sexual, or bloodborne routes. To date, there is 1 cluster of possible fecal-respiratory transmission.

5. Cats and ferrets can be infected and transmit to each other, but there are no reported cases to date of transmission to humans; minks transmit to each other and to humans.

Routes of Transmission

SARS-CoV-2 is spread predominantly via virus-containing droplets through sneezing, coughing, or when people interact with each other for some time in close proximity (usually less than one metre) (ECDC 2020, Chan JF 2020, Li Q 2020, Liu Y 2020). These droplets can then be inhaled or land on surfaces where they can be detectable for up to four hours on copper, up to 24 hours on cardboard and up to two to three days on plastic and stainless steel (van Doremalen 2020, Aboubakr 2020). Other people may come into contact with these droplets and get infected when they touch their nose, mouth or eyes (Wang Y 2020, Deng W 2020). SARS-CoV-2 environmental contamination around COVID-19 patients is extensive, and hospital IPC procedures should account for the risk of fomite, and potentially airborne, transmission of the virus (Santarpia 2020).

Respiratory transmission

SARS-CoV-2 is transmitted via (macro-)droplets greater than 5-10 μm in diameter, commonly referred to as **respiratory droplets**, and via smaller particles, < 5 μm in diameter, which are referred to as droplet nuclei or **aerosols**. The almost century-old dichotomy (Wells 1934) “droplets vs. aerosol transmission” has been challenged by SARS-CoV-2. It is now accepted that there is no real evidence that SARS-CoV-2 pathogens should be carried *only in large droplets* (Fennelly 2020). At the beginning of the current pandemic, aerosol transmission of SARS-CoV-2 was generally not accepted; however, over the months, it became evident that some COVID-19 clusters, for example in choirs (Hamner 2020, Miller 2020), shopping malls (Cai J 2020), restaurants (Li Y 2020 + Lu J 2020), meat processing plants (Günter 2020, The Guardian) or vertically aligned flats connected by drainage pipes in the master bathrooms (Kang M 2020, Gormley 2020), were best explained by aerosol transmission.

On July 9 2020, WHO updated its information about SARS-CoV-2 transmission (WHO 20200709), “There have been reported outbreaks of COVID-19 in some closed settings, such as restaurants, nightclubs, places of worship or places of work where people may be shouting, talking, or singing. In these outbreaks, aerosol transmission, particularly in these indoor locations where there are crowded and inadequately ventilated spaces where infected persons spend long periods of time with others, cannot be ruled out.” In the preceding days,

a group of more than 200 scientists led by Lidia Morawska and Donald K. Milton had published a three-page warning: *It is Time to Address Airborne Transmission of COVID-19* (see also LM's [first alert on 10 April](#) and the overviews by [Prather, Wang and Schooley](#) as well as [Jayaweera 2020](#) et al.). As always, discordant views have been voiced, arguing that long-range aerosol-based transmission is not the dominant mode of SARS-CoV-2 transmission ([Klompas 2020](#)) and that the main mode of transmission of SARS-CoV-2 is short range through droplets and close contact ([Chagla 2020](#)). Today, aerosol transmission of SARS-CoV-2 is an accepted notion.

Viruses are released during exhalation, talking, and coughing in micro-droplets small enough to remain aloft in the air and pose a risk of exposure at distances beyond 1 to 2 m from an infected individual ([Morawska 2020b](#)). [Morawska, Milton et al.](#) suggested the following measures to mitigate airborne transmission of SARS-CoV-2:

- Provide sufficient and effective ventilation (supply clean outdoor air, minimize recirculating air) particularly in public buildings, workplace environments, schools, hospitals, and retirement care homes.
- Supplement general ventilation with airborne infection controls such as local exhaust, high efficiency air filtration, and germicidal ultraviolet lights.
- Avoid overcrowding, particularly in public transport and public buildings.

A precautionary approach to COVID-19 prevention is shown in Table 1.

The evidence for aerosol transmission and resulting recommendations for prevention have been sublimely summarized by [Prather et al.](#) in five sentences: "Respiratory infections occur through the transmission of virus-containing droplets (>5 to $10\ \mu\text{m}$) and aerosols ($\leq 5\ \mu\text{m}$) exhaled from infected individuals during breathing, speaking, coughing, and sneezing. Traditional respiratory disease control measures are designed to reduce transmission by droplets produced in the sneezes and coughs of infected individuals. However, a large proportion of the spread of coronavirus disease 2019 (COVID-19) appears to be occurring through airborne transmission of aerosols produced by asymptomatic individuals during breathing and speaking ([Morawska 2020](#), [Anderson 2020](#), [Asadi 2019](#)). Aerosols can accumulate, remain infectious in indoor air for hours, and be easily inhaled deep into the lungs. For society to resume, measures designed to reduce aerosol transmission must be implemented, including universal masking and regular, widespread testing to identify and isolate infected asymptomatic individuals ([Prather 2020](#))."

Table 1. Reducing the transmission of SARS-CoV-2

Transmission route	Prevention
1. (Macro-)Droplets (> 5 µm)	Face masks + social distancing
2. Aerosol (micro-droplets, ≤ 5µm)	<ul style="list-style-type: none">• Face masks• Improved ventilation (open doors and windows; upgrade ventilation systems)• Improved air filtering• Avoidance of crowded and closed spaces
3. Fomites	Handwashing

For mechanical systems, organizations such as ASHRAE (the American Society of Heating, Ventilating, and Air Conditioning Engineers) and REHVA (the Federation of European Heating, Ventilation and Air Conditioning Associations) have provided guidelines based on the existing evidence of airborne transmission (Morawska 2020b).

A recent demonstration of aerosol production visualizes speech-generated oral fluid droplets and underlines that even normal speaking may be an important mode of transmission (Bax 2020). The authors provide videos showing speech droplets emitted by four people, when speaking the phrase “spit happens” with the face positioned about 10–15 cm behind a thin sheet of intense green laser light (video: <https://www.youtube.com/watch?v=ooVjNth4ut8>). Previously, experimental support for aerosol transmission of SARS-CoV-2 came from studies that visualized droplet formation at the exit of the mouth during violent expiratory events such as sneezing and coughing (Scharfman 2016, Bourouiba 2020; see also the video). These studies showed that the lifetime of a droplet could be considerably longer than previously assumed. When analyzed with highly sensitive laser light scattering, loud speech was found to be able to emit thousands of oral fluid droplets per second which could linger in the air for minutes (Anfinrud 2020, Stadnytskyi 2020; see also the movies showing the experimental setup and the critical comment by Abbas 2020). Loud and persistent shouting as would be usual in noisy, closed and stagnant air environments (meat packing facilities, discos, pubs, etc.) is now believed to produce the same number of droplets as produced by coughing (Chao 2020). Speech and other vocal activities such as singing have also been shown to generate air particles, with the rate of emission corresponding to voice loudness (Asadi 2019).

Of note, during the 2003 SARS epidemic, an airborne route of transmission also appeared to be a plausible explanation for the so-called Amoy Garden outbreak. On that occasion, the virus was aerosolized within the confines of very small bathrooms and may have been inhaled, ingested or

transmitted indirectly by contact with fomites as the aerosol settled (WHO 2003).

Recognizing that SARS-CoV-2 is transmitted via aerosol has even more far-reaching consequences – personal, professional, societal and economic – in situations of community COVID-19 outbreaks. At the personal level (reminder: 20% of infected individuals are thought to transmit 80% of SARS-CoV-2 cases, so minimizing the probability of coming close to such super-spreader individuals is imperative), people might wish to avoid prolonged meetings with people from outside their inner-core “friends-and-family-bubble”; inside the bubble, meetings should be restricted to a handful of people. For everyday life, the following five *rules of thumb* are helpful:

6. Wear face masks in public spaces.
7. Keep a distance of 2 (two!) meters to other people.
8. Avoid **crowded** places (more than 5-10 people).
9. Avoid in particular **crowded** and **closed** spaces (even worse: air-conditioned closed places where air is being moved around).
10. Avoid in any circumstances **crowded**, **closed** and **noisy** spaces where people must shout to communicate. These are SARS-CoV-2’s preferred playgrounds.

At the professional level, healthcare workers will require nothing short of optimal protection. As N95 respirators achieve better filtration of airborne particles than medical masks, they should be recommended for all inpatient care of patients with COVID-19, not only during aerosol generating procedures (Dau 2020). Guideline recommendations that do not support N95 use for all inpatient COVID-19 management should consider reevaluating the existing data.

At the societal level, the attendance of important biographic events such as weddings, baptisms, circumcisions and funerals may need to be limited to a handful of intimate friends and family (probably less than 10). Religious services and recreational activities such as team sport and choir singing may not be possible.

At the economic level, all activities which bring numerous people from outside the “friends-and-family-bubbles” together may be banned during new community outbreaks. Instead of complete lockdowns like those enacted during the spring of 2020 – and which are not economically sustainable – partial lockdowns would target places where strangers or simply unacquainted people meet: discos, amusement parks, bars, restaurants, brothels and many more. Other activities such as meat processing plants might need major re-

structuring before resuming work. [Re-opening schools in September](#) has been and remains a world-wide challenge.

If SARS-CoV-2 is transmitted airborne for several meters, previous prevention recommendations of frequent hand-washing and maintaining a distance of at least one meter (arm's length) ([WHO 20200329](#)) are insufficient. Instead, adequate control measures would include wearing suitable masks whenever infected persons may be nearby and providing adequate ventilation of enclosed spaces where such persons are known to be or may recently have been ([Morawska 2020](#), [Somsen 2020](#), [Meselson 2020](#)). Infrastructure may have to be adjusted, for example, Heating, Ventilation and Air Conditioning Systems (HVAC) in buildings and on ships ([Correia 2020](#), [Gormley 2020](#)). Most of all, tighter prevention recommendations will have unforeseeable consequences for all places where foreigners, strangers or simply unacquainted people meet. SARS-CoV-2 will thus continue to impact cultural and economic life – theaters, cinemas, bars, restaurants, shops, etc – for some time to come.

In the meantime, the discussion about SARS-CoV-2 and aerosols continues. Even the droplet/aerosol terminology has now been questioned by advocates of a new distinction between aerosols and droplets using a size threshold of 100 μm , not the historical 5 μm ([Prather 2020](#)). The authors argue that this size more effectively separates their aerodynamic behavior, ability to be inhaled, and efficacy of interventions. Viruses in droplets (larger than 100 μm) typically fall to the ground in seconds within 2 m of the source and can be sprayed like tiny cannonballs onto nearby individuals. Recently, a fourth transmission route has been hypothesized: *aerosolized fomites*. In this case, virus would remain viable in the environment, on materials like paper tissues and on the bodies of living animals, long enough to be aerosolized on non-respiratory dust particles that can transmit infection through the air to new mammalian hosts ([Asadi 2020](#)). In retrospective, we will one day understand that transmission of viruses is not the only conceptual framework upset by the SARS-CoV-2 virus.

Fomites

It is still unclear to which extent transmission via fomites (e.g., elevator buttons, hand rails, restroom taps) is epidemiologically relevant ([Cai J 2020](#)). [A fomite is any inanimate object that, when contaminated with or exposed to infectious agents such as a virus, can transfer a disease to another person.] SARS-CoV-2 seems omnipresent in the spaces inhabited by infected individuals. A protein-rich medium like airway secretions could protect the virus when it is expelled and may enhance its persistence and transmission by contaminated fomites ([Pastorino 2020](#)). For example, SARS-CoV-2 RNA was de-

tected from 58 out of 601 samples (10%) from case cabins 1-17 days after the cabins were vacated, but not from non-case cabins (Yamagishi 2020). There was no difference in the detection proportion between cabins for symptomatic (15%, 28/189) and asymptomatic cases (21%, 28/131). However, no SARS-CoV-2 virus was isolated from any of the samples. Potential drivers of the SARS-CoV-2 surface adsorption and stability in various environmental conditions have been recently discussed (Joonaki 2020).

Recently, the role of fomites in SARS-CoV-2 transmission has been questioned. Some authors find that the chance transmission through inanimate surfaces might be less frequent than hitherto assumed (Mondelli 2020) and less likely to occur in real-life conditions, provided that standard cleaning procedures and precautions are enforced. Transmission through fomites would occur only in instances where an infected person coughs or sneezes on the surface, and someone else touches that surface soon after the cough or sneeze (within 1–2 h) (Goldman 2020). In any case, even face coverings may protect indirectly against fomite transmission. After analyzing mask-wearing and face-touching behavior in public areas, one group found that mask wearing was associated with reduced face-touching behavior, especially touching of the eyes, nose, and mouth (Chen Y 2020). They conclude that the reduction of face-touching behaviors by mask wearing could contribute to curbing the COVID-19 pandemic.

Mother-to-child

See the chapter *Pediatrics*, page 408.

Stool, urine

Although no cases of fecal-oral transmission of SARS-CoV-2 have been reported thus far, a study from Zhuhai reports prolonged presence of SARS-CoV-2 viral RNA in fecal samples. Of the 41 (55%) of 74 patients with fecal samples that were positive for SARS-CoV-2 RNA, respiratory samples remained positive for SARS-CoV-2 RNA for a mean of 17 days and fecal samples remained positive for a mean of 28 days after first symptom onset (Wu Y 2020). In another study, 22/133 patients, SARS-CoV-2 was still detected in the sputum or feces (up to 39 and 13 days, respectively) after pharyngeal swabs became negative (Chen 2020). In still another study, seven out of ten children contained SARS-CoV-2 virus RNA in their fecal specimens, despite all patients showing negative results in respiratory tract specimens and the median time from onset to having negative results in respiratory tract and fecal specimens was 9 days and 34.43 days, respectively (Du W 2020).

Until proof of the contrary, the possibility of fecal-oral transmission should not be excluded. Strict precautions must be observed when handling the stools of patients infected with coronavirus. Sewage from hospitals should also be properly disinfected (Yeo 2020). Fortunately, antiseptics and disinfectants such as ethanol or bleach have good activity on human coronaviruses (Geller 2012). During the SARS-CoV outbreak in 2003, where SARS-CoV was shown to survive in sewage for 14 days at 4°C and for 2 days at 20°C (Wang XW 2005), environmental conditions could have facilitated this route of transmission.

Blood products

SARS-CoV-2 is rarely detected in blood (Wang W 2020, Wolfel 2020). After screening of 2430 donations in real-time (1656 platelet and 774 whole blood), authors from Wuhan found plasma samples positive for viral RNA from 4 asymptomatic donors (Chang 2020). It remains unclear whether detectable RNA signifies infectivity.

In a Korean study, seven asymptomatic blood donors were later identified as COVID-19 cases. None of 9 recipients of platelets or red blood cell transfusions tested positive for SARS-CoV-2 RNA (Kwon 2020). More data are needed before transmission through transfusion can be declared safe.

Sexual transmission

It is unknown whether purely sexual transmission is possible. Scrupulously eluding infection via fomites and respiratory droplets during sexual intercourse would suppose remarkable acrobatics many people might not be willing to perform. Reassuringly, SARS-CoV-2 doesn't seem to be present in semen (Guo L 2020).

Cats and dogs et al.

SARS-CoV-2 can be transmitted to cats and dogs (Newman 2020, Garigliany 2020). When inoculated with SARS-CoV-2, cats can transmit the virus to other cats (Halfmann 2020) and although none of the cats showed symptoms, all shedded virus for 4 to 5 days and developed antibody titers by day 24. In another report, two out of fifteen dogs from households with confirmed human cases of COVID-19 in Hong Kong were found to be infected. The genetic sequences of viruses from the two dogs were identical to the virus detected in the respective human cases (Sit 2020). In still another paper, 817 companion animals in northern Italy at the height of the spring 2020 epidemic were tested for SARS-CoV-2. Although no animals tested PCR positive, 3.4% of dogs and 3.9% of cats had measurable SARS-CoV-2 neutralizing antibody titers, with

dogs from COVID-19 positive households being significantly more likely to test positive than those from COVID-19 negative households (Patterson 2020).

Evidence of infection of animals with SARS-CoV-2 has been shown experimentally both *in vivo* and *in vitro* for monkeys, cats, ferrets, rabbits, foxes, and hamsters (Edwards 2020). While computational models also predicted infectivity of pigs and wild boar (Santini 2020), a recent study suggested that pigs and chickens could not be infected intranasally or oculo-oronasally by SARS-CoV-2 (Schlottau 2020).

At present, it seems unlikely that animals are potential intermediate hosts in the chain of human–pet–human transmission. Only special circumstances, such as the high animal population densities encountered on infected mink farms, might put humans at risk of animal-to-human transmission. In any case, persons with COVID-19 should be advised to avoid contact with animals. Companion animals that test positive for SARS-CoV-2 should be monitored and separated from persons and other animals until they recover (Newman 2020).

Transmission Event

Transmission of a virus from one person to another depends on four variables:

1. The nature of the **virus**;
2. The nature of the **transmitter**;
3. The nature of the **transmittee** (the person who will become infected);
4. The transmission **setting**.

Virus

In order to stay in the evolutionary game, all viruses have to overcome a series of challenges. They must attach to cells; fuse with their membranes; release their nucleic acid into the cell; manage to make copies of themselves; and have the copies exit the cell to infect other cells. In addition, respiratory viruses must make their host cough and sneeze to get back into the environment again. Ideally, this happens before the hosts realize that they are sick. This is all the more amazing as SARS-CoV-2 is more like a piece of computer code than a living creature *in sensu strictu* (its 30,000 DNA base pairs are a mere 100,000th of the human genetic code). That doesn't prevent the virus from being ferociously successful:

- It attaches to the human angiotensin converting enzyme 2 (ACE2) receptor (Zhou 2020) which is present not only in nasopharyngeal and oropharyngeal

ryngeal mucosa, but also in lung cells, such as in type II pneumocytes. SARS-CoV-2 thus combines the high transmission rates of the common coronavirus NL63 (infection of the upper respiratory tract) with the severity of SARS in 2003 (lower respiratory tract);

- It has a relatively long incubation time of around 5 days (influenza: 1-2 days), thus giving it more time to spread;
- It is transmitted by asymptomatic individuals.

As mentioned above, SARS-CoV-2 can be viable for days ([van Doremalen 2020](#)). Environmental factors that might influence survival of the virus outside the human body will be discussed below (page 112).

The virologic determinants of more or less successful SARS-CoV-2 transmission are not yet fully understood.

Transmittor

The mean incubation of SARS-CoV-2 infection is around 5 days ([Lauer 2020](#), [Li 2020](#), [Zhang J 2020](#), [Pung 2020](#)), comparable to that of the coronaviruses causing SARS or MERS ([Virlogeux 2016](#)). Almost all symptomatic individuals will develop symptoms within 14 days of infection ([Bai Y 2020](#)). Infectiousness seems to peak on or before symptom onset ([He X 2020](#)).

It is currently unknown if SARS-CoV-2 transmission correlates with the following characteristics of the index case (transmittor):

- Symptom severity;
- Large concentrations of virus in the upper and lower respiratory tract;
- SARS-CoV-2 RNA in plasma;
- In the future: reduced viral load due to drug treatment (like in people treated for HIV infection) [[Cohen 2011](#), [Cohen 2016](#), [LeMessurier 2018](#)]

There are some first hints that symptom severity of the index case has an impact on transmission probability. In one study of 3410 close contacts of 391 SARS-CoV-2 infected index cases, the secondary attack rate increased with the severity of index cases, from 0.3% for asymptomatic to 3.3% for mild, 5.6% for moderate, and 6.2% for severe or critical cases ([Luo L 2020](#)). Index cases with expectoration were associated with higher risk for secondary infection (13.6% vs. 3.0% for index cases without expectoration).

SARS-CoV-2 transmission certainly correlates with a still ill-defined “**super-spreader** status” of the infected individual. For unknown reasons, some individuals are remarkably contagious, capable of infecting dozens or hundreds of people, possibly because they breathe out many more particles than others

when they talk (Asadi 2019), shout, cough or sneeze. Transmission of SARS-CoV and MERS-CoV as well occurred to a large extent by means of super-spreading events (Peiris 2004, Hui 2018). Super-spreading has been recognized for years to be a normal feature of disease spread (Lloyd-Smith 2005). One group suggested that 80% of secondary transmissions could be caused by around 20% of infectious individuals (Adam 2020). A value called the dispersion factor (k) describes this phenomenon. The lower the k is, the more transmission comes from a small number of people (Kupferschmidt 2020, Tufekci 2020; if you like the FT, read also *To beat Covid-19, find today's super-spreading 'Typhoid Marys'*). While SARS was estimated to have a k of 0.16 (Lloyd-Smith 2005) and MERS of 0.25, in the flu pandemic of 1918, in contrast, the value was about one, indicating that clusters played less of a role (Endo 2020). For the SARS-CoV-2 pandemic, the dispersion factor (k) is currently thought to be higher than for SARS and lower than for the 1918 influenza (Endo 2020, Miller 2020, On Kwok 2020, Wang L 2020).

Transmission is more likely when the infected individual has few or no symptoms because no one will take notice and maintain precautions. Around half of secondary cases are supposed to be transmitted during the pre-symptomatic stage of the index case (He X 2020). **Asymptomatic transmission** of SARS-CoV-2 – proven a few weeks after the beginning of the pandemic (Bai Y 2020) – has justly been called the Achilles' heel of the COVID-19 pandemic (Gandhi 2020). As shown during an outbreak in a skilled nursing facility, the percentage of asymptomatic individuals can be as high as 50% early (Arons 2020; most of these individuals would later develop some symptoms). Importantly, SARS-CoV-2 viral load was comparable in individuals with typical and atypical symptoms, and in those who were pre-symptomatic or asymptomatic. Seventeen of 24 specimens (71%) from pre-symptomatic persons had viable virus by culture 1 to 6 days before the development of symptoms (Arons 2020), suggesting that SARS-CoV-2 may be shed at high concentrations before symptom development.

Note that although SARS-CoV-2 is highly transmissible, given the right circumstances and the right prevention precautions, **zero transmission** is possible. In one case report, there was no evidence of transmission to 16 close contacts, among them 10 high-risk contacts, from a patient with mild illness and positive tests for up to 18 days after diagnosis (Scott 2020).

To what extent **children** contribute to the spread of SARS-CoV-2 infection in a community is unknown. Infants and young children are normally at high risk for respiratory tract infections. The immaturity of the infant immune system may alter the outcome of viral infection and is thought to contribute to the severe episodes of influenza or respiratory syncytial virus infection in

this age group (Tregoning 2010). Until now, however, there is a surprising absence of pediatric patients with COVID-19, something that has perplexed clinicians, epidemiologists, and scientists (Kelvin 2020).

Although a retrospective study among individuals hospitalized in Milan showed that only about 1% of children and 9% of adults without any symptoms or signs of SARS-CoV-2 infection tested positive for SARS-CoV-2 (Milani 2020) – suggesting a minor role of children in transmission –, children can be the source for important outbreaks. Twelve children who acquired SARS-CoV-2 infection in child-care facilities – all with mild or no symptoms – transmitted the virus to at least 12 (26%) of 46 non-facility contacts (Lopez 2020). Family gatherings are well-known settings for widespread SARS-CoV-2 transmission. In an outbreak that occurred during a 3-week family gathering of five households, an adolescent aged 13 years was the suspected primary patient. Among the 14 persons who stayed in the same house, 12 experienced symptoms (Schwartz 2020). Of note, none of the additional six family members who maintained outdoor physical distance without face masks during two longer visits (10 and 3 hours) to the family gathering developed symptoms.

Health authorities should know that SARS-CoV-2 infected individuals do not need to be **quarantined** for weeks. Persistently positive RT-PCRs generally do not reflect replication-competent virus. SARS-CoV-2 infectivity rapidly decreases to near-zero after about 10 days in mild-to-moderately-ill patients and 15 days in severely-to-critically-ill and immunocompromised patients (Rhee 2020). Of note, RT-PCR cycle threshold (Ct) values (a measure for viral load) correlated strongly with cultivable virus. In one study, the probability of culturing virus declined to 8% in samples with Ct > 35 and to 6% (95% CI: 0.9–31.2%) 10 days after onset; it was similar in asymptomatic and symptomatic persons (Singanayagam 2020).

In any potential transmission setting, **face coverings** reduce the transmission of SARS-CoV-2. Among 139 clients exposed to two symptomatic hair stylists with confirmed COVID-19 while both the stylists and the clients wore face masks, not a single symptomatic secondary case was observed; among 67 clients tested for SARS-CoV-2, all tests were negative (Hendrix 2020). At least one hair stylist was infectious: all four close household contacts (presumably without masks) became ill. Unfortunately, face masks don't work everywhere – and not for everyone. In some countries, infected individuals claimed the right to not wear face coverings in the name of liberty (they forgot that an individual's liberty ends where it infringes on the liberties of others). Interestingly, social distancing compliance can be predicted by individual differences in **working memory** (WM) capacity. WM retains a limited amount of information over a short period of time at the service of other ongoing men-

tal activities. Limited WM capacity constrains mental functions while extended capacities are often associated with better cognitive and affective outcomes. The hidden message in the paper by Weizhen Xie et al: if the guy sitting next to you in the bus does not wear a mask, don't insist. His working memory capacity is poor (Xie W 2020). Change seats.

Transmittee

Upon exposure to SARS-CoV-2, the virus may come in contact with cells of the upper or lower respiratory tract of an individual. After inhalation, larger respiratory droplets are filtered by the nose or deposited in the oropharynx, whereas smaller droplet nuclei are carried by the airstream into the lungs where their site of deposition depends on their mass, size and shape and is governed by various mechanisms (Dhand 2020).

Numerous cell entry mechanisms of SARS-CoV-2 have been identified that potentially contribute to the immune evasion, cell infectivity, and wide spread of SARS-CoV-2 (Shang J 2020). Susceptibility to SARS-CoV-2 infection is probably influenced by the host genotype. This would explain the higher percentage of severe COVID-19 in men (Piccininni 2020) and possibly the similar disease course in some twins in the UK (The Guardian, 5 May 2020).

A high percentage of SARS-CoV-2 seronegative individuals have SARS-CoV-2 reactive T cells. This is explained by previous exposure to other coronaviruses ("common cold" coronaviruses) which have proteins that are highly similar to those of SARS-CoV-2. It is still unclear whether these cross-reactive T cells confer some degree of protection, are inconsequential or even potentially harmful if someone who possesses these cells becomes infected with SARS-CoV-2 (Braun 2020, Grifoni 2020).

The "right" genotype may not be sufficient in the presence of massive exposure, for example by numerous infected people and on multiple occasions as might happen, for example, in health care institutions being overwhelmed during the beginning of an epidemic. It is known from other infectious diseases that viral load can influence the incidence and severity of disease. Although the evidence is limited, high infection rates among health workers have been attributed to more frequent contact with infected patients, and frequent exposure to excreta with high viral load (Little 2020).

Recently, it has been shown that rigorous social distancing not only slowed the spread of SARS-CoV-2 in a cohort of young, healthy adults but also prevented symptomatic COVID-19 while still inducing an immune response (Bielecki 2020). After an outbreak in two Swiss army companies (company 2 and 3, see Table 2), 62% of tested soldiers were found to have been exposed to

SARS-CoV-2 and almost 30% had COVID-19 symptoms. In company 1 where strict distancing and hygiene measures (SDHMs) had been implemented after the outbreak in companies 2 and 3, only 15% had exposure to SARS-CoV-2, but none of them had COVID-19 symptoms. (The Swiss army SDHMs: keep a distance of at least 2 m from each other at all times; wear a surgical face mask in situations where this can not be avoided [e.g., military training]; enforce a distance of 2 m between beds and during meals; clear and disinfect all sanitary facilities twice daily; separate symptomatic soldiers immediately.)

Table 2: Baseline characteristics of the study population on March 31, 2020

	Company 1	Company 2	Company 3	Company 2+3
Soldiers	154	200	154	354
Tested*	88	130	51	181
Exposed to SARS-CoV-2**	13/88 (15%)	83/130 (64%)	30/51 (59%)	113/181 (62%)
COVID-19***	0 (0%)	54/200 (27%)	48/154 (31%)	102/354 (29%)

* More than 50% of the soldiers of all companies were sampled on April 14.

** On April 14, detection of SARS-CoV-2 in nasopharyngeal swabs or by positive serology test for immunoglobulin A, G or M.

*** Symptomatic patients between March 11 and May 3, 2020.

The authors cautiously suggested that quantitatively reducing the viral inoculum received by SARS-CoV-2 virgin recipients not only reduced the probability of infection but also could have caused asymptomatic infections in others while still being able to induce an immunological response ([Bielecki 2020](#)), and idea that was later echoed by Monica Gandhi and George W. Rutherford ([Ghandi 2020](#)).

If genes offer no protection, behavior may do so. In the coming autumn and winter months 2020/2021, face covering is paramount. It reduces, for example, the number of infections among hospital personnel. In March 2020, the Mass General Brigham, the largest health care system in Massachusetts (12 hospitals, > 75,000 employees), implemented universal masking of all HCWs and patients with surgical masks. During the pre-intervention period, the SARS-CoV-2 positivity rate increased exponentially, with a case doubling time of 3.6 days. During the intervention period, the positivity rate decreased linearly from 14.65% to 11.46% ([Wang X 2020](#)). In Paris, in a 1500-bed adult and a 600-bed pediatric setting of a university hospital, the total number of HCW cases peaked on March 23rd, then decreased slowly, concomitantly with a continuous increase in preventive measures (including universal medical

masking and PPE) (Contejean 2020). In Chennai, India, before the introduction of face shields, 12/62 workers were infected while visiting 5880 homes with 31,164 persons (222 positive for SARS-CoV-2). After the introduction of shields among 50 workers (previously uninfected) who continued to provide counseling, visiting 18,228 homes with 118,428 persons (2682 positive), no infection occurred (Bhaskar 2020). The preventive measures are not new to medicine – surgeons have been using personal protective equipment (PPE) for more than a century (Stewart 2020). The wearing of masks by adults also remains critical to reducing transmission in child-care settings (Link-Gelles 2020).

Masks work even with super-emitters. By measuring outward emissions of micron-scale aerosol particles by healthy humans performing various expiratory activities, William D. Ristenpart, Sima Asadi and colleagues found that both surgical masks and unvented KN95 respirators reduced the outward particle emission rates by 90% and 74% on average during speaking and coughing. These masks similarly decreased the outward particle emission of a coughing super-emitter, who for unclear reasons emitted up to two orders of magnitude more expiratory particles via coughing than average (Asadi 2020). An interesting collateral finding is that people speak more loudly, but do not cough more loudly, when wearing a mask.

After visualizing the flow fields of coughs under various mouth covering scenarios, a recently published study (Simha 2020) found that

1. N95 masks are the most effective at reducing the horizontal spread of a cough (spread: 0.1 and 0.25 meters).
2. A simple disposable mask can reduce the spread to 0.5 meters, while an uncovered cough can travel up to 3 meters.
3. **Coughing into the elbow is** not very effective. Unless covered by a sleeve, a bare arm cannot form the proper seal against the nose necessary to obstruct airflow and a cough is able to leak through any openings and propagate in many directions.

Although the data regarding the effectivity of face masks is now clear, will everyone understand, i.e., even individuals with a still functioning working memory? If some individuals continue to put themselves at risk of SARS-CoV-2 infection (as well as their friends and relatives in case of infection), what are the drivers of behaviors that might influence risk for COVID-19 exposure among young adults? In a remote US county, the drivers were low severity of disease outcome; peer pressure; and exposure to misinformation, conflicting messages, or opposing views regarding masks (Wilson 2020). A scientifically inspired national prevention policy will be needed to counter misinformation

and – let’s speak frankly for just two seconds! – address human stupidity. First, public health officials need to ensure that the public understands clearly when and how to wear cloth face coverings properly. Second, innovation is needed to extend physical comfort and ease of use. Third, the public needs consistent, clear, and appealing messaging that normalizes community masking (Brooks 2020). A small adaption in our daily lives relies on a highly effective low-tech solution that can help turn the tide.

Transmission setting

The transmission setting, i.e., the actual place where the transmission of SARS-CoV-2 occurs, is the final element in the succession of events that leads to the infection of an individual. High population density which facilitates super-spreading events (see also chapter *Epidemiology, Transmission Hotspots*, page 23) is key to widespread transmission of SARS-CoV-2.

In the early phase of the pandemic, hospitals and other health care centers have sometimes been hotspots of SARS-CoV-2 transmission, either because of ignorance or missing protective equipment. In a major London teaching hospital, 66/435 (15%) of COVID-19 inpatient cases between 2 March and 12 April 2020 were definitely or probably hospital-acquired through varied transmission routes (case fatality: 36%) (Rickman 2020).

In a prospective international multicentre cohort study of 1718 healthcare workers participating in 5148 at-risk tracheal intubation episodes, the overall incidence of the primary endpoint (lab-confirmed COVID-19 diagnosis or new symptoms requiring self-isolation or hospitalisation) was 10.7% over a median of 32 days (El-Boghdadly 2020).

In Greece, healthcare personnel represented approximately 10% of all notified COVID-19 cases. Those with high-risk occupational exposure to COVID-19 had increased probability of serious morbidity, healthcare seeking, hospitalization and absenteeism (Maltezou 2020).

In the University of Washington medical system and its affiliated organizations, between March 12 and April 23, a total of 3477 symptomatic employees were tested; 185 (5.3%) employees tested positive for COVID-19. The prevalence of SARS-CoV-2 was similar when comparing frontline HCWs (5.2%) to non-frontline staff (5.5%) (Mani 2020).

Awaiting results from (difficult) randomised trials, the currently best available evidence suggests for all public and healthcare settings (Chu DK 2020) the *FPE protection triad* of

- Physical distancing of at least 1 m, even better 2 m.
- Face mask, ideally N95 or similar.
- Eye protection (mandatory in health care settings and similar).

Find a helpful video, demonstrating the complex procedure for putting on and removing PPE as recommended by the CDC ([Ortega 2020](#)). It is safe and cheap to assume that SARS-CoV-2 is everywhere ([Lednicky 2020](#)).

Indoor environments

Indoor environments are SARS-CoV-2's preferred playgrounds. In one modeling study, the authors estimated that viral load concentrations in a room with an individual who was coughing frequently were very high, with a maximum of 7.44 million copies/m³ from an individual who was a high emitter ([Riediker 2020](#)). However, regular breathing from an individual who was a high emitter was modeled to result in lower room concentrations of up to 1248 copies/m³. They conclude that the estimated infectious risk posed by a person with typical viral load who breathes normally was low and that only a few people with very high viral load posed an infection risk in the poorly ventilated closed environment simulated in this study.

Clusters of cases have been reported in many, predominantly indoor, settings. Viable virus from air samples was isolated from samples collected 2 to 4.8 meters away from two COVID-19 patients ([Lednicky 2020](#)). The genome sequence of the SARS-CoV-2 strain isolated was identical to that isolated from the NP swab from the patient with an active infection. Estimates of viable viral concentrations ranged from 6 to 74 TCID₅₀ units/L of air. During the first months of the pandemic, most clusters were found to involve fewer than 100 cases, with the exceptions being in healthcare (hospitals and elderly care), large religious gatherings and large co-habitation settings (worker dormitories and ships). Other settings with examples of clusters between 50–100 cases in size were schools, sports, bars, shopping centers and a conference ([Leclerc 2020](#)).

Transportation in closed spaces – by bus, train or aircraft – has been shown to transmit SARS-CoV-2 at various degrees, depending on face mask use and time of travel. One paper describes a **bus** ride in a vehicle 11,3 meters long and 2,5 meters wide with 49 seats, fully occupied with all windows closed and the ventilation system on during the 2,5-hour trip. Among the 49 passengers (including the driver) who shared the ride with the index person, eight tested positive and eight developed symptoms. The index person sat in the second-to-last row, and the infected passengers were distributed over the middle and rear rows ([Luo K 2020](#)). An even more informative paper describes 68 individ-

uals (including the source patient) taking a bus on a 100-minute round trip to attend a worship event. In total, 24 individuals (35%) received a diagnosis of COVID-19 after the event. The authors were able to identify seats for each passenger and divided bus seats into high-risk and low-risk zones (Shen Y 2020). Passengers in the high-risk zones had moderately but non-significantly higher risk of getting COVID-19 than those in the low-risk zones. On the 3-seat side of the bus, except for the passenger sitting next to the index patient, none of the passengers sitting in seats close to the bus window developed infection. In addition, the driver and passengers sitting close to the bus door also did not develop infection, and only 1 passenger sitting by an operable window developed infection. The absence of a significantly increased risk in the part of the bus closer to the index case suggested that airborne spread of the virus may at least partially explain the markedly high attack rate observed. Lesson learned for the future? If you take the bus, choose seats near a window – and open it!

To answer the question how risky **train** traveling is in the COVID-19 era, one group analyzed passengers in Chinese high-speed trains. They quantified the transmission risk using data from 2334 index patients and 72,093 close contacts who had co-travel times of 0–8 hours from 19 December 2019 through 6 March 2020. Unsurprisingly, travelers adjacent to an index patient had the highest attack rate (3.5%) and the attack rate decreased with increasing distance but increased with increasing co-travel time. The overall attack rate of passengers with close contact with index patients was 0.32% (Hu M 2020).

A recently published review about **in-flight** transmission of SARS-CoV-2 finds that the absence of large numbers of confirmed and published in-flight transmissions of SARS-CoV is encouraging but not definitive evidence that fliers are safe (Freedman 2020). At present, based on circumstantial data, strict use of masks appears to be protective. In previous studies, SARS-CoV-2 transmission has been described onboard aircrafts (Chen J 2020, Hoehl 2020). Note that if you don't wear a mask, business class will not protect you from infection. A Vietnamese group report on a cluster among passengers on VN54 (Vietnam Airlines), a 10-hour commercial flight from London to Hanoi on March 2, 2020 (at that time, the use of face masks was not mandatory on airplanes or at airports) (Khanh 2020). Affected persons were passengers, crew, and their close contacts. The authors traced 217 passengers and crew to their final destinations and interviewed, tested, and quarantined them. Among the 16 persons in whom SARS-CoV-2 infection was detected, 12 (75%) were passengers seated in business class along with the only symptomatic person (attack rate 62%). Seating proximity was strongly associated with increased infection risk (risk ratio 7.3, 95% CI 1.2–46.2).

Transmission clusters, partly linked to super-spreader events, have been reported since the very beginning of the SARS-CoV-2 pandemic:

- Business meeting, Southern Germany, 20-21 January (Rothe 2020)
- Cruise Ship, Yokohoma, Japan, 4 February (Rocklov 2020)
- Church meeting, Daegu, Korea, 9 and 16 February (Kim 2020)
- Religious gathering, Mulhouse, France, 17-24 February (Kuteifan 2020)
- Medical advisory board meeting, Munich, Germany, 20-21 (Hijnen 2020)
- Nursing facility, King County, Washington, 28 February (McMichael 2020)
- Aircraft carriers: Theodore Roosevelt (Payne 2020) + Charles-de-Gaulle, March (Le Monde)
- Choir (Hamner 2020)
- Concert (Plautz 2020)
- Homeless shelter, Boston, 28 March (Baggett 2020)

A study of 1407 transmission pairs that formed 643 transmission clusters in mainland China identified 34 super-spreaders, with 29 super-spreading events occurring outside households (Xu XK 2020).

Temperature and climate

Another variable still poorly understood is ambient temperature and humidity.

SARS-CoV-1 (2003): The transmission of coronaviruses can be affected by several factors, including the climate (Hemmes 1962). Looking back to the 2003 SARS epidemic, we find that the stability of the first SARS virus, SARS-CoV, depended on temperature and relative humidity. A study from Hong Kong, Guangzhou, Beijing, and Taiyuan suggested that the SARS outbreak in 2002/2003 was significantly associated with environmental temperature. The study provided some evidence that there was a higher possibility for SARS to reoccur in spring than in autumn and winter (Tan 2005). It was shown that SARS-CoV remained viable for more than 5 days at temperatures of 22-25°C and relative humidity of 40-50%, that is, typical air-conditioned environments (Chan KH 2011). However, viability decreased after 24 h at 38°C and 80-90% relative humidity. The better stability of SARS coronavirus in an environment of low temperature and low humidity could have facilitated its transmission in subtropical areas (such as Hong Kong) during the spring and in air-conditioned environments. It might also explain why some Asian countries in the tropics (such as Malaysia, Indonesia or Thailand) with high tem-

perature and high relative humidity environment did not have major community SARS outbreaks ([Chan KH 2011](#)).

SARS-CoV-2 (2020): It is as yet unclear as to whether and to what extent climatic factors influence virus survival outside the human body and might influence local epidemics. SARS-CoV-2 is not readily inactivated at room temperature and by drying like other viruses, for example herpes simplex virus. One study mentioned above showed that SARS-CoV-2 can be detectable as an aerosol (in the air) for up to three hours, up to four hours on copper, up to 24 hours on cardboard and up to two to three days on plastic and stainless steel ([van Doremalen 2020](#)).

A few studies suggest that low temperature might enhance the transmissibility of SARS-CoV-2 ([Wang 2020b](#), [Tobías 2020](#)) and that the arrival of summer in the northern hemisphere could reduce the transmission of the COVID-19. A possible association of the incidence of COVID-19 and both reduced solar irradiance and increased population density has been discussed ([Guasp 2020](#)). It was reported that simulated sunlight rapidly inactivated SARS-CoV-2 suspended in either simulated saliva or culture media and dried on stainless steel plates while no significant decay was observed in darkness over 60 minutes ([Ratnesar-Shumate 2020](#)). However, another study concluded that transmission was likely to remain high even at warmer temperatures ([Sehra 2020](#)). In particular the current epidemics in Brazil and India and the southern US – areas with high temperatures – should temper hopes that COVID “simply disappears like a miracle”. Warm and humid summer conditions alone might be unlikely to limit substantially new important outbreaks ([Luo 2020](#), [Baker 2020](#), [Collins 2020](#)).

Outlook

Almost a year after the first SARS-CoV-2 outbreak in China, the transmission dynamics driving the pandemic are coming into focus. It now appears that a high percentage (as high as 80%?) of secondary transmissions could be caused by a small fraction of infectious individuals (10 to 20%?; [Adam 2020](#)); if this is the case, then the more people are grouped together, the higher the probability that a superspreader is part of the group.

It is now acknowledged that aerosol transmission plays an important role in SARS-CoV-2 transmission ([Morawska 2020b](#), [WHO 20200709](#), [Prather 2020](#)); if this is the case, then building a wall around this same group of people and putting a ceiling above them further enhances the probability of SARS-CoV-2 infection.

It finally appears that shouting and speaking loudly emits thousands of oral fluid droplets per second which could linger in the air for minutes ([Anfinrud 2020](#), [Stadnytskyi 2020](#), [Chao 2020](#), [Asadi 2019](#), [Bax 2020](#)); if this is the case, then creating noise (machines, music) around people grouped in a closed environment would create the perfect setting for a superspreader event.

Over the coming months, the scientific community will try and

- define more precisely the role of fomites in the transmission of SARS-CoV-2;
- unravel the secrets of super-spreading;
- advance our understanding of host factors involved in the successful “seeding” of SARS-CoV-2 infection;
- elucidate the role of children in the transmission of the virus at the community level;
- explicate the role of young adults in the genesis of the second European SARS-CoV-2 wave;
- continue to describe the conditions under which people should be allowed to gather in larger groups;

Without a coronavirus vaccine, nobody will return to a “normal” pre-2020 way of life. The most promising exit strategy for the coronavirus crisis is an efficient vaccine that can be rolled out safely and affordably to billions of people. Thousands of researchers are working around the clock, motivated by fame (becoming the next [Dr. Salk](#)?) and money (becoming the next [Scrooge McDuck](#)?). Until the worldwide availability of a vaccine, the only feasible prevention scheme is a potpourri of physical distancing ([Kissler 2020](#)), intensive testing, case isolation, contact tracing, quarantine ([Ferretti 2020](#)) and, as a last (but not impossible) resort, local lockdowns and curfews.

New References (5th Edition)

The following pages add short comments to the papers published since the previous edition (June-October). The comments are from <https://covidreference.com/daily-science>. The complete list of references starts at page 131.

The Virus

Zhou J, Otter JA, Price JR, et al. **Investigating SARS-CoV-2 surface and air contamination in an acute healthcare setting during the peak of the COVID-19 pandemic in London.** Clin Infect Dis. 2020 Jul 8;ciaa905. PubMed: <https://pubmed.gov/32634826>. Full-text: <https://doi.org/10.1093/cid/ciaa905>

In a cross-sectional observational study in a London hospital, SARS-CoV-2 was detected on 114/218 (52.3%) of surfaces and 14/31 (38.7%) air samples but no virus was cultured. As expected, viral RNA was more likely to be found in areas immediately occupied by COVID-19 patients than in other areas (Zhou J 2020).

Schlottau K, Rissmann M, Graaf A, et al. **SARS-CoV-2 in fruit bats, ferrets, pigs, and chickens: an experimental transmission study.** Lancet Microbe July 07, 2020. Full-text: [https://doi.org/10.1016/S2666-5247\(20\)30089-6](https://doi.org/10.1016/S2666-5247(20)30089-6)

When intranasally inoculated with TCID₅₀ of a SARS-CoV-2 isolate, twelve fruit bats (*Rousettus aegyptiacus*) showed characteristics of a reservoir host and 12 ferrets (*Mustela putorius*) mimicked subclinical human infection with efficient spread. Pigs (*Sus scrofa domestica*) and 20 chickens (*Gallus gallus domestica*) could not be infected by SARS-CoV-2 (Schlottau 2020).

Routes of Transmission

Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. **Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors.** Ann Intern Med 2020, published 17 September. Full-text: <https://doi.org/10.7326/M20-5008>

Eric Meyerowitz et al. present a comprehensive review of the evidence of human SARS-CoV-2 transmission (Meyerowitz 2020). Their key points:

1. Respiratory transmission is the dominant mode of transmission.
2. Vertical transmission occurs rarely; transplacental transmission has been documented.
3. Cats and ferrets can be infected and transmit to each other, but there are no reported cases to date of transmission to humans; minks transmit to each other and to humans.
4. Direct contact and fomite transmission are presumed but are likely only an unusual mode of transmission.
5. Although live virus has been isolated from saliva and stool and viral RNA has been isolated from semen and blood donations, there are no reported cases of SARS-CoV-2 transmission via fecal-oral, sexual, or bloodborne routes. To date, there is 1 cluster of possible fecal-respiratory transmission.

AEROSOL, DROPLETS

Prather KA, Marr LC, Schooley RT, et al. **Airborne transmission of SARS-CoV-2.** Science 05 Oct 2020: eabf0521. Full-text: <https://doi.org/10.1126/science.abf0521>

According to Kimberly Prather and colleagues, we should clarify the terminology to distinguish between aerosols and droplets using a size threshold of 100 μm , not the historical 5 μm (Prather 2020). This size more effectively separates their aerodynamic behavior, ability to be inhaled, and efficacy of interventions. Viruses in droplets (larger than 100 μm) typically fall to the ground in seconds within 2 m of the source and can be sprayed like tiny cannonballs onto nearby individuals.

Bax A, Bax CE, Stadnytskyi V, Anfinrud P. **SARS-CoV-2 transmission via speech-generated respiratory droplets.** Lancet Inf Dis September 11, 2020. Full-text: [https://doi.org/10.1016/S1473-3099\(20\)30726-X](https://doi.org/10.1016/S1473-3099(20)30726-X)

Spit happens. This group published the impressive NEJM video, visualizing speech-generated oral fluid droplets and suggesting that normal speaking might be an important mode of transmission (Bax 2020). Here, the four authors vigorously resist the criticism of other authors who argued that the video experiments were unrealistic. They also provide nice new videos showing speech droplets emitted by four people, when speaking the phrase “spit happens” with the face positioned about 10–15 cm behind a thin sheet of intense green laser light.

Anfinrud P, Stadnytskyi V, Bax CE, Bax A. **Visualizing Speech-Generated Oral Fluid Droplets with Laser Light Scattering.** N Engl J Med. 2020 May 21;382(21):2061-2063. PubMed: <https://pubmed.gov/32294341>. Full-text: <https://doi.org/10.1056/NEJMc2007800>

New video: <https://www.youtube.com/watch?v=ooVjNth4ut8>

Fennelly KP. **Particle sizes of infectious aerosols: implications for infection control.** Lancet Respir Med, July 24, 2020. Full-text: [https://doi.org/10.1016/S2213-2600\(20\)30323-4](https://doi.org/10.1016/S2213-2600(20)30323-4)

Is there really evidence that some pathogens are carried *only in large droplets*? (Fennelly 2020) Or would cough aerosols and exhaled breath from patients with various respiratory infections show striking similarities in aerosol size distributions? In case of doubt, how would you protect your family and yourself?

Santarpia JL, Rivera DN, Herrera VL et al. **Aerosol and surface contamination of SARS-CoV-2 observed in quarantine and isolation care.** Sci Rep 10, 12732 (2020). Full-text: <https://doi.org/10.1038/s41598-020-69286-3>

After evacuation from the Diamond Princess cruise ship in March 2020, 11 were admitted to a hospital in Nebraska, two in a biocontainment unit and 9 in a quarantine unit. Key features of both units included: (1) individual rooms with private bathrooms; (2) negative-pressure rooms (> 12 ACH) and negative-pressure hallways; (3) key-card access control; (4) unit-specific infection prevention and control (IPC) protocols including hand hygiene and changing of gloves between rooms; and (5) personal protective

equipment (PPE) for staff that included contact and aerosol protection. [Joshua Santarpia](#) and colleagues collected air and surface samples to examine viral shedding from isolated individuals and detected viral contamination among all samples. Their data suggest that **SARS-CoV-2 environmental contamination around COVID-19 patients is extensive**, and hospital IPC procedures should account for the risk of fomite, and potentially airborne, transmission of the virus ([Santarpia 2020](#)).

Klompas M, Baker MA, Rhee C. **Airborne Transmission of SARS-CoV-2: Theoretical Considerations and Available Evidence**. JAMA. 2020 Aug 4;324(5):441-442. PubMed: <https://pubmed.gov/32749495> . Full-text: <https://doi.org/10.1001/jama.2020.12458>

Brief review. It is impossible to conclude that aerosol-based transmission never occurs, write [Michael Klompas](#) and colleagues, but the balance of currently available evidence suggests that long-range **aerosol-based transmission is not the dominant mode** of SARS-CoV-2 transmission ([Klompas 2020](#)).

Chagla Z, Hota S, Khan S, Mertz D; International Hospital and Community Epidemiology Group. **Airborne Transmission of COVID-19**. Clin Infect Dis. 2020 Aug 11;ciaa1118. PubMed: <https://pubmed.gov/32780799>. Full-text: <https://doi.org/10.1093/cid/ciaa1118>

[Zain Chagla](#) and colleagues discuss the paper by Morawska L, Milton DK, *It is Time to Address Airborne Transmission of COVID-19* (Clin Infect Dis 2020, 6 July). They agree that there is potential for the transmission by aerosols, especially in poorly ventilated indoor crowded environments. However, they argue that the **main mode of transmission of SARS-CoV-2 is short range through droplets and close contact**. Explore this one-page comment to see how the debate continues ([Chagla 2020](#)).

Asadi S, Gaaloul ben Hnia N, Barre RS, et al. **Influenza A virus is transmissible via aerosolized fomites**. Nat Commun 11, 4062 (2020). Full-text: <https://doi.org/10.1038/s41467-020-17888-w>

SARS-CoV-2 can be transmitted via droplets, fomites and possibly aerosol. Will we need to get accustomed to a fourth transmission route, **aerosolized fomites**? That's what [Nicole Bouvier](#) and colleagues suggest, although for now only for influenza A virus. They show that dried influenza virus remains viable in the environment, on materials like paper tissues and on the bodies of living animals, long enough to be aerosolized on non-respiratory dust particles that can transmit infection through the air to new mammalian hosts ([Asadi 2020](#)). Will we soon see a paper about SARS-CoV-2 transmission via aerosolized fomites?

Kang M, Wi J, Yuan J, et al. **Probable Evidence of Fecal Aerosol Transmission of SARS-CoV-2 in a High-Rise Building**. Ann Intern Med 2020, published 1 September. Full-text: <https://doi.org/10.7326/M20-0928>

Nanshan Zhong, Min Kang and colleagues report 9 infected patients in 3 families. While the first family had a history of travel to the coronavirus disease 2019 (COVID-19) epicenter Wuhan, the other 2 families had no travel history and a later onset of symptoms. The families lived in 3 vertically aligned flats connected by drainage pipes in the master bathrooms. The authors suggest that virus-containing fecal aerosols may have been produced in the associated vertical stack during toilet flushing after use by the index patients (Kang M 2020). This report reminds us of a SARS-1 outbreak in March 2003 among residents of Amoy Gardens, Hong Kong, with a total of 320 SARS cases in less than three weeks (see www.SARSReference.com, page 65).

See also the comment by Michael Gormley [Gormley M. **SARS-CoV-2: The Growing Case for Potential Transmission in a Building via Wastewater Plumbing Systems.** Ann Intern Med 2020, published 1 September. Full-text: <https://doi.org/10.7326/M20-6134>] concludes that that wastewater plumbing systems, particularly those in high-rise buildings, deserve closer investigation, both immediately in the context of SARS-CoV-2 and in the long term, because they may be a reservoir for other harmful pathogens.

FOMITES

Mondelli MU, Colaneri M, Seminari E, et al. **Low risk of SARS-CoV-2 transmission by fomites in real-life conditions.** Lancet Infect Dis September 29, 2020. Full-text: [https://doi.org/10.1016/S1473-3099\(20\)30678-2](https://doi.org/10.1016/S1473-3099(20)30678-2)

Some arguments that environmental contamination leading to SARS-CoV-2 transmission is unlikely to occur in real-life conditions, provided that standard cleaning procedures and precautions are enforced. The chance of transmission through inanimate surfaces is likely less frequent than hitherto recognized (Mondelli 2020).

Yamagishi T, Ohnishi M, Matsunaga N, et al. **Environmental sampling for severe acute respiratory syndrome coronavirus 2 during COVID-19 outbreak in the Diamond Princess cruise ship.** J Infect Dis. 2020 Jul 21;jiaa437. PubMed: <https://pubmed.gov/32691828>. Full-text: <https://doi.org/10.1093/infdis/jiaa437>

In the early epidemic in Japan, many infections occurred among the passengers and crew members on board the *Diamond Princess* cruise ship in February, 2020. By March 1, 2020, there were approximately 700 individuals with laboratory-detected SARS-CoV-2 infection (see the previous articles by Russell et al., Yamagishi et al. and Tabata et al.). The authors performed environmental sampling on the Diamond Princess cruise ship on 22-23 February 2020 (prior to disinfection of the vessel and while some passengers and crew members remained aboard) and obtained specimens from cabins in which confirmed COVID-19 cases stayed (case cabins), cabins with no confirmed case at any point (non-case cabins), and common areas. SARS-CoV-2 RNA was detected from 58 out of 601 samples (10%) **from case cabins 1-17 days after the cabins were vacated**, but not from non-case cabins (Yamagishi 2020). There was no difference in the detection proportion between cabins for symptomatic (15%, 28/189) and asymp-

tomatic cases (21%, 28/131). No SARS-CoV-2 virus was isolated from any of the samples. The authors conclude that transmission risk of SARS-CoV-2 from symptomatic and asymptomatic patients may be similar and environmental surfaces could be involved in viral transmission.

Chen Y, Qin G, Chen J, et al. **Comparison of Face-Touching Behaviors Before and During the Coronavirus Disease 2019 Pandemic.** JAMA Netw Open 2020;3(7):e2016924. <https://doi.org/10.1001/jamanetworkopen.2020.16924>

Is wearing face masks really associated with reduced face-touching behaviors? To answer the question, Xing Li and colleagues from Sun Yat-sen University, Guangzhou, China, used videos recorded in public transportation stations, streets, and parks among the general population in China, Japan, South Korea, Western Europe (ie, England, France, Germany, Spain, and Italy), and the US to analyze mask-wearing and face-touching behavior in public areas. The authors found that mask wearing was associated with reduced face-touching behavior, especially touching of the eyes, nose, and mouth (Chen Y 2020). They conclude that the reduction of face-touching behaviors by mask wearing could contribute to curbing the COVID-19 pandemic. Excellent news for the coming months.

Joonaki E, Hassanpouryouzband A, Heldt Cl, et al. **Surface Chemistry Can Unlock Drivers of Surface Stability of SARS-CoV-2 in Variety of Environmental Conditions.** Chem, August 06, 2020. Full-text: <https://doi.org/10.1016/j.chempr.2020.08.001>

Nice overview of existing knowledge concerning viral spread, molecular structure of SARS-CoV-2, and the stability of the virus surface. Edris Joonaki and colleagues discuss potential drivers of the SARS-CoV-2 surface adsorption and stability in various environmental conditions (Joonaki 2020).

Deng W, Bao L, Gao H, et al. **Ocular conjunctival inoculation of SARS-CoV-2 can cause mild COVID-19 in rhesus macaques.** Nat Commun 11, 4400 (2020). Full-text: <https://doi.org/10.1038/s41467-020-18149-6>

If you are exploring extra-respiratory routes of SARS-CoV-2 transmission, read the article by Chuan Qin, Wei Deng and colleagues. The authors inoculated five rhesus macaques with SARS-CoV-2 conjunctivally, intratracheally, and intragastrically. The *conjunctivally* infected animal had a higher viral load in the nasolacrimal system than the *intratracheally* infected animal but also showed mild interstitial pneumonia, suggesting distinct viral distributions (Deng W 2020).

MOTHER-TO-CHILD

Vivanti AJ, Vauloup-Fellous C, Prevot S, et al. **Transplacental transmission of SARS-CoV-2 infection.** Nat Commun 2020. Full-text: <https://doi.org/10.1038/s41467-020-17436-6>

Maybe the first documented case of transplacental transmission. French doctors report on a 23-year-old COVID-19 patient who gave birth by cesarean section to a baby found to have the infection (Vivanti 2020). The viral load was much higher in the placental tissue than in the amniotic fluid or maternal blood: this suggests the presence of the virus in placental cells, which is consistent with findings of inflammation seen at histological examination. Good news: baby is fine.

Chambers C, Krogstad P, Betrand K, et al. **Evaluation for SARS-CoV-2 in Breast Milk From 18 Infected Women.** JAMA August 19, 2020. Full-text: <https://doi.org/10.1001/jama.2020.15580>

There are some case reports on the detection of SARS-CoV-2 in breast milk. Christina Chambers and colleagues examined 64 breast milk samples from 18 infected women. Although SARS-CoV-2 RNA was detected in one milk sample, the viral culture for that sample was negative. These data suggest that SARS-CoV-2 RNA does not represent replication-competent virus and that breast milk may not be a source of infection for the infant (Chambers 2020).

CATS AND DOGS

Patterson EI, Elia G, Grassi A, et al. **Evidence of exposure to SARS-CoV-2 in cats and dogs from households in Italy.** bioRxiv 23 July 2020. Full-text: <https://doi.org/10.1101/2020.07.21.214346>

Nicola Decaro and colleagues assess SARS-CoV-2 infection in 817 companion animals in northern Italy at the height of the spring 2020 epidemic. Although no animals tested PCR positive, 3.4% of dogs and 3.9% of cats had measurable SARS-CoV-2 neutralizing antibody titers, with dogs from COVID-19 positive households being significantly more likely to test positive than those from COVID-19 negative households (Patterson 2020). From their experience, the authors conclude that it is unlikely that infected pets play an active role in SARS-CoV-2 transmission to humans. Only under special circumstances, such as the high animal population densities encountered on infected mink farms, animal-to-human transmission might be likely.

Garigliany M, Van Laere AS, Clercx C, et al. **SARS-CoV-2 Natural Transmission from Human to Cat, Belgium, March 2020.** Emerg Infect Dis. 2020 Aug 12;26(12). PubMed: <https://pubmed.gov/32788033>. Full-text: <https://doi.org/10.3201/eid2612.202223>

Mutien Garigliany from Liège, Belgium, and colleagues report a human-to-cat transmission. A household cat was productively infected with the SARS-CoV-2 virus excreted by its owner, and the infection caused a non-fatal but nevertheless severe disease (Garigliany 2020).

Transmission Event

TRANSMITTER

Rockett RJ, Arnott A, Lam C, et al. **Revealing COVID-19 transmission in Australia by SARS-CoV-2 genome sequencing and agent-based modeling.** Nat Med 2020 Jul 9. PubMed: <https://pubmed.gov/32647358>. Full-text: <https://doi.org/10.1038/s41591-020-1000-7>

These researchers examined the added value of near real-time genome sequencing of SARS-CoV-2 in a subpopulation of infected patients during the first 10 weeks of COVID-19 containment in Australia. **Genomic evidence was used to cluster 38.7% (81 out of 209) of cases for which the available epidemiological data could not identify direct links (Rockett 2020).** This included clustering 12.4% (26 out of 209) of cases with a history of recent arrival from overseas with other cases without a travel history and 5.3% (11/209) of locally acquired cases with unknown epidemiological links. Twenty-two (10.5%) of the 209 cases were epidemiologically classified as 'locally acquired—contact not identified'.

Park YJ, Choe YJ, Park O, et al. **Contact Tracing during Coronavirus Disease Outbreak, South Korea, 2020.** Emerg Infect Dis October 2020. Full-text: https://wwwnc.cdc.gov/eid/article/26/10/20-1315_article

The authors analyzed 59,073 contacts of 5,706 COVID-19 index patients. Of 10,592 household contacts, 11.8% had COVID-19; rates were higher for contacts of children than adults. Of 48,481 non-household contacts, 1.9% had COVID-19. Interestingly, the highest COVID-19 rate (18.6%) was found for household contacts of school-aged children (Park YJ 2020) and the lowest (5.3%) for household contacts of children 0–9 years in the middle of school closure.

Milani GP, Bottino I, Rocchi A, et al. **Frequency of Children vs Adults Carrying Severe Acute Respiratory Syndrome Coronavirus 2 Asymptotically.** JAMA Pediatr. Published online September 14, 2020. Full-text: <https://doi.org/10.1001/jamapediatrics.2020.3595>

Early reports suggested that children, often asymptomatic, might be facilitators of SARS-CoV-2 transmission and amplify local outbreaks. Here, Carlo Agostini, Gregorio Milani and colleagues conducted a study among individuals hospitalized in Milan. About 1% of children and 9% of adults without any symptoms or signs of SARS-CoV-2 infection tested positive for SARS-CoV-2. The authors conclude that their data do not support the hypothesis that children are at higher risk of carrying SARS-CoV-2 asymptotically than adults (Milani 2020). Attention: a retrospective analysis.

Luo L, Liu D, Liao X, et al. **Contact Settings and Risk for Transmission in 3410 Close Contacts of Patients With COVID-19 in Guangzhou, China: A Prospective Cohort Study.** Ann Intern Med. 2020 Aug 13. PubMed: <https://pubmed.gov/32790510>. Full-text: <https://doi.org/10.7326/M20-2671>

Chen Mao and colleagues traced 3410 close contacts of 391 SARS-CoV-2 infected index cases between 13 January and 6 March 2020. 127 contacts (3.7%) were secondarily infected. Compared with the household setting (10.3%), the secondary attack rate was lower for exposures in healthcare settings (1.0%) and on public transportation (0.1%). **Interestingly, although not unexpectedly, the secondary attack rate increased with the severity of index cases, from 0.3% for asymptomatic to 3.3% for mild, 5.6% for moderate, and 6.2% for severe or critical cases (Luo L 2020).** Index cases with expectoration were associated with higher risk for secondary infection (13.6% vs. 3.0% for index cases without expectoration).

Xie W, Campbell S, Zhang W. **Working memory capacity predicts individual differences in social-distancing compliance during the COVID-19 pandemic in the United States.** Proc Natl Acad Sci U S A. 2020 Jul 10;202008868. PubMed: <https://pubmed.gov/32651280>. Full-text: <https://doi.org/10.1073/pnas.2008868117>

Among 850 US residents participating in a survey, the authors found that social distancing compliance could be predicted by individual differences in working memory (WM) capacity. WM retains a limited amount of information over a short period of time at the service of other ongoing mental activities. Its limited capacity constrains our mental functions, such that higher WM capacity is often associated with better cognitive and affective outcomes. Of note, the unique contribution of WM capacity to the individual differences in social distancing compliance could not be explained by other psychological and socioeconomic factors (e.g., moods, personality, education, and income levels). The message that the authors hide using scientific language can be said more clearly: if you see a guy sitting in the bus not wearing a mask: poor idiot, don't get closer. His WM capacity is poor (Xie W 2020).

Rhee C, Kanjilal S, Baker M, et al. **Duration of SARS-CoV-2 Infectivity: When is it Safe to Discontinue Isolation?** Clinical Infectious Diseases, 25 August 2020, ciaa1249. Full-text: <https://doi.org/10.1093/cid/ciaa1249>

Persistently positive RT-PCRs generally do not reflect replication-competent virus. SARS-CoV-2 infectivity rapidly decreases thereafter to near-zero after about 10 days in mild-to-moderately-ill patients and 15 days in severely-to-critically-ill and immunocompromised patients (Rhee 2020). This review summarizes evidence-to-date on the duration of **infectivity** of SARS-CoV-2.

Singanayagam A, Patel M, Charlett A. **Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020.** Euro Surveill. 2020;25(32). Full-text: <https://doi.org/10.2807/1560-7917.ES.2020.25.32.2001483>

More on “viral load” and infectivity. Virus culture was attempted from 324 samples (from 253 cases) that tested positive for SARS-CoV-2 by RT-PCR. RT-PCR cycle threshold (Ct) values correlated strongly with cultivable virus. Probability of culturing virus

declined to 8% in samples with Ct > 35 and to 6% (95% CI: 0.9–31.2%) 10 days after onset; it was similar in asymptomatic and symptomatic persons (Singanayagam 2020).

Lesho E, Reno L, Newhart D, et al. **Temporal, Spatial, and Epidemiologic Relationships of SARS-CoV-2 Gene Cycle Thresholds: A Pragmatic Ambi-directional Observation.** *Clinical Infectious Diseases*, 25 August 2020, ciaa1248. Full-text: <https://doi.org/10.1093/cid/ciaa1248>

Same direction. This prospective serial sampling of 70 patients revealed clinically relevant cycle thresholds (Ct, “viral load”), namely a Ct of 24 (“high viral load”), 34, and > 40 (“negative”) that occurred 9, 26, and 36 days after symptom onset. Of note, race, gender, or corticosteroids did not appear to influence RNA-positivity. A retrospective analysis of 180 patients revealed that initial Ct did not correlate with requirement for admission or intensive care (Lesho 2020).

Lopez AS, Hill M, Antezano J, et al. **Transmission Dynamics of COVID-19 Outbreaks Associated with Child Care Facilities — Salt Lake City, Utah, April–July 2020.** *MMWR Morb Mortal Wkly Rep.* ePub: 11 September 2020. Full-text: <http://dx.doi.org/10.15585/mmwr.mm6937e3>

Cuc Tran, Adriana Lopez and colleagues describe 12 children who acquired SARS-CoV-2 infection in child-care facilities. All had mild or no symptoms. They transmitted the virus to at least 12 (26%) of 46 non-facility contacts (Lopez 2020). The authors conclude that testing children who might not have symptoms could improve control of transmission from child-care attendees to family members.

Schwartz NG, Moorman AC, Makaretz A, et al. **Adolescent with COVID-19 as the Source of an Outbreak at a 3-Week Family Gathering — Four States, June–July 2020.** *MMWR Morb Mortal Wkly Rep.* ePub: 5 October 2020. Full-text: <http://dx.doi.org/10.15585/mmwr.mm6940e2>

Children can serve as the source for COVID-19 outbreaks, even when their symptoms are mild (Schwartz 2020). In this outbreak that occurred during a 3-week family gathering of five households, an adolescent aged 13 years was the suspected primary patient. Among the 14 persons who stayed in the same house, 12 experienced symptoms. Of note, none of the additional six family members who maintained outdoor physical distance without face masks during two longer visits (10 and 3 hours) to the family gathering developed symptoms.

TRANSMITTEE

Lewis NM, Chu VT, Ye D, et al. **Household Transmission of SARS-CoV-2 in the United States.** *Clinical Infectious Diseases*, 16 August 2020. Full-text: <https://doi.org/10.1093/cid/ciaa1166>

Nathaniel M Lewis and colleagues sought to estimate the household secondary infection rate (SIR) of SARS-CoV-2 and evaluate potential risk factors for secondary infection among 58 households in Utah and Wisconsin. Fifty-two of 188 household contacts acquired secondary infections (SIR: 28%, 95% CI: 22–34%). Of note, household contacts to COVID-19 patients with immunocompromised conditions had increased odds of infection (OR: 15.9, 95% CI: 2.4–106.9) as well as household contacts who themselves had diabetes mellitus (OR: 7.1, 95% CI: 1.2–42.5) (Lewis 2020).

Wilson RF, Sharma AJ, Schluechtermann S, et al. **Factors Influencing Risk for COVID-19 Exposure Among Young Adults Aged 18–23 Years — Winnebago County, Wisconsin, March–July 2020.** MMWR Morb Mortal Wkly Rep. ePub: 9 October 2020. DOI: <http://dx.doi.org/10.15585/mmwr.mm6941e2>

Still in the US: Which are the drivers of behaviors that might influence risk for COVID-19 exposure among young adults? In a remote US County, these were low severity of disease outcome; peer pressure; and exposure to misinformation, conflicting messages, or opposing views regarding masks (Wilson 2020). A scientifically inspired national prevention policy would have been helpful.

Asadi S, Cappa CD, Barreda S, et al. **Efficacy of masks and face coverings in controlling outward aerosol particle emission from expiratory activities.** Sci Rep 10, 15665 (2020). Full-text: <https://doi.org/10.1038/s41598-020-72798-7>

Masks work with super-emitters! William D. Ristenpart, Sima Asadi and colleagues measured outward emissions of micron-scale aerosol particles by healthy humans performing various expiratory activities while wearing different types of medical-grade or homemade masks. Both surgical masks and unvented KN95 respirators reduced the outward particle emission rates by 90% and 74% on average during speaking and coughing. These masks similarly decreased the outward particle emission of a coughing super-emitter, who for unclear reasons emitted up to two orders of magnitude more expiratory particles via coughing than average (Asadi 2020). An interesting collateral finding: people speak more loudly, but do not cough more loudly, when wearing a mask.

Hendrix MJ, Walde C, Findley K, Trotman R. **Absence of Apparent Transmission of SARS-CoV-2 from Two Stylists After Exposure at a Hair Salon with a Universal Face Covering Policy — Springfield, Missouri, May 2020.** MMWR Morb Mortal Wkly Rep. 14 July 2020. Full-text: <http://dx.doi.org/10.15585/mmwr.mm6928e2>

Have we ever mentioned masks? Among 139 clients exposed to two symptomatic hair stylists with confirmed COVID-19 while both the **stylists** and the clients wore face masks, not a single symptomatic secondary case was observed; among 67 clients tested for SARS-CoV-2, all tests were negative (Hendrix 2020). At least one hair stylist was infectious: all four close household contacts (presumably without masks) became ill.

Wang X, Ferro EG, Zhou G, Hashimoto D, Bhatt DL. **Association Between Universal Masking in a Health Care System and SARS-CoV-2 Positivity Among Health Care Workers.** JAMA. 2020 Jul 14. PubMed: <https://pubmed.gov/32663246>. Full-text: <https://doi.org/10.1001/jama.2020.12897>

Again, universal masking: in March 2020, the Mass General Brigham, the largest health care system in Massachusetts (12 hospitals, > 75,000 employees), implemented **universal masking of all HCWs** and patients with surgical masks. During the preintervention period, the SARS-CoV-2 positivity rate increased exponentially, with a case doubling time of 3.6 days. During the intervention period, the positivity rate decreased linearly from 14.65% to 11.46%, with a weighted mean decline of 0.49% per day and a net slope change of 1.65% additional decline per day compared with the preintervention period (Wang X 2020).

Contejean A, Leporrier J, Canouï E, et al. **Comparing dynamics and determinants of SARS-CoV-2 transmissions among health care workers of adult and pediatric settings in central Paris.** Clin Infect Dis. 2020 Jul 15:ciaa977. PubMed: <https://pubmed.gov/32663849>. Full-text: <https://doi.org/10.1093/cid/ciaa977>

This prospective study compared a 1,500-bed adult and a 600-bed pediatric setting of a university hospital located in central Paris. From February 24th until April 10th, 2020, all symptomatic HCW were screened. Attack rates were of 3.2% and 2.3% in the adult and pediatric setting, respectively ($p = 0.0022$). In the adult setting, HCW more frequently reported exposure to COVID-19 patients **without PPE** (25% versus 15%, $p = 0.046$) (Contejean 2020). The total number of HCW cases peaked on March 23rd, then decreased slowly, concomitantly with a continuous increase in preventive measures (including universal medical masking and PPE). Residual transmissions were related to exposures with undiagnosed patients or colleagues but not to contacts with children attending out-of-home care facilities.

Brooks JT, Butler JC, Redfield RR. **Universal Masking to Prevent SARS-CoV-2 Transmission—The Time Is Now.** JAMA July 14, 2020. Full-text: <https://doi.org/10.1001/jama.2020.13107>

Data is clear now. First, public health officials need to ensure that the public understands clearly when and how to wear cloth face coverings properly. Second, innovation is needed to extend physical comfort and ease of use. Third, the public needs consistent, clear, and appealing messaging that normalizes community masking (Brooks 2020). According to the authors, **broad adoption of cloth face coverings is a civic duty**, a small adaption in our daily lives reliant on a highly effective low-tech solution that can help turn the tide.

Stewart CL, Thornblade LW, Diamond DJ, Fong Y, Melstrom LG. **Personal Protective Equipment and COVID-19: A Review for Surgeons.** Ann Surg. 2020 Aug;272(2):e132-e138. PubMed: <https://pubmed.gov/32675516>. Full-text: <https://doi.org/10.1097/SLA.0000000000003991>

Are you a surgeon? Then your particular medical association has been **using personal protective equipment (PPE) for more than a century** (Stewart 2020). This review addresses both the mechanism of SARS-CoV-2 transmission and the capabilities of PPE in the perioperative COVID-19 setting.

Bhaskar ME, Arun S. **SARS-CoV-2 Infection Among Community Health Workers in India Before and After Use of Face Shields**. JAMA August 17, 2020. Full-text: <https://doi.org/10.1001/jama.2020.15586>

This observational study describes transmission before and after the use of face shields (made of polyethylene terephthalate) in health workers in Chennai, India. Before the introduction of face shields, 12/62 workers were infected, while visiting 5,880 homes with 31,164 persons (222 positive for SARS-CoV-2). After the introduction, among 50 workers (previously uninfected) who continued to provide counseling, visiting 18,228 homes with 118,428 persons (2682 positive), no infection occurred (Bhaskar 2020).

Link-Gelles R, DellaGrotta AL, Molina C, et al. **Limited Secondary Transmission of SARS-CoV-2 in Child Care Programs — Rhode Island, June 1–July 31, 2020**. MMWR Morb Mortal Wkly Rep. ePub: 21 August 2020. Full-text: <http://dx.doi.org/10.15585/mmwr.mm6934e2>

Ruth Link-Gelles et al. report a possible secondary transmission in four of the 666 child-care programs in Rhode Island that were allowed to reopen. The apparent absence of secondary transmission within the other 662 child-care programs was likely the result of efforts to contain SARS-CoV-2 transmission, in particular maximum class sizes and use of face masks for adults (Link-Gelles 2020). The authors conclude that adherence to current CDC recommendations remains critical to reducing transmission in child-care settings, **including wearing of masks by adults**, limiting mixing between established student-teacher groups, staying home when ill, and cleaning and disinfecting frequently touched surfaces.

Simha PP, Rao PSM. **Universal trends in human cough airflows at large distances featured**. Physics of Fluids 32, 081905 (2020). Published 25 August. Full-text: <https://doi.org/10.1063/5.0021666>

Fine droplets can pass through layers of masks and are carried away by the exhaled airflow unlike larger droplets that settle down due to gravity. Now Padmanabha Prasanna Simha and Prasanna Simha Mohan Rao visualize the flow fields of coughs under various mouth covering scenarios. The results:

1. N95 masks are the most effective at reducing the horizontal spread of a cough (spread: 0.1 and 0.25 meters).
2. A simple disposable mask can reduce the spread to 0.5 meters, while an uncovered cough can travel up to 3 meters.

3. **Coughing into the elbow?** Not very effective! Unless covered by a sleeve, a bare arm cannot form the proper seal against the nose necessary to obstruct airflow and a cough is able to leak through any openings and propagate in many directions (Prasanna Simha 2020).

TRANSMISSION SETTING

Gebrekidan S, Bennhold K, Apuzzo M, Kirkpatrick DD. **Ski, Party, Seed a Pandemic: The Travel Rules That Let Covid-19 Take Flight.** The New York Times 2020 published 1 October. Full-text: <https://www.nytimes.com/2020/09/30/world/europe/ski-party-pandemic-travel-coronavirus.html>

ISCHGL, Austria — They came from across the world to ski in the most famous resorts of the Austrian alps... (Gebrekidan 2020).

Lednický JA, Lauzardo M, Hugh Fan Z, et al. **Viable SARS-CoV-2 in the air of a hospital room with COVID-19 patients.** Int J Infect Dis. 2020 Sep 16:S1201-9712(20)30739-6. PubMed: <https://pubmed.gov/32949774>. Full-text: <https://doi.org/10.1016/j.ijid.2020.09.025>

John A. Lednický and colleagues isolated viable virus from air samples collected 2 to 4.8 meters away from two COVID-19 patients (Lednický 2020). The genome sequence of the SARS-CoV-2 strain isolated was identical to that isolated from the NP swab from the patient with an active infection. Estimates of viable viral concentrations ranged from 6 to 74 TCID₅₀ units/L of air.

Freedman DO, Wilder-Smith A. **In-flight Transmission of SARS-CoV-2: a review of the attack rates and available data on the efficacy of face masks.** Journal of Travel Medicine September 25. Full-text: <https://doi.org/10.1093/jtm/taaa178>.

Review of outbreaks during flights. According to the authors, the absence of large numbers of confirmed and published in-flight transmissions of SARS-CoV is encouraging but not definitive evidence that fliers are safe. At present, based on circumstantial data, strict use of masks appears to be protective (Freedman 2020). Structured prospective studies to quantitate transmission risk on flight with rigid masking protocols are now most pressing.

Khanh NC, Thai PQ, Quach H-L, Thi NA-H, Dinh PC, Duong TN, et al. **Transmission of severe acute respiratory syndrome coronavirus 2 during long flight.** Emerg Infect Dis 2020, published 18 September. Full-text: <https://doi.org/10.3201/eid2611.203299>

The authors report a cluster of cases among passengers on VN54 (Vietnam Airlines), a 10-hour commercial flight from London to Hanoi on March 2, 2020. Among the 16 persons in whom SARS-CoV-2 infection was detected, 12 (75%) were passengers seated in business class along with the only symptomatic person (attack rate 62%) (Khanh 2020). The authors find that blocking middle seats, currently recommended by the airline

industry, may in theory prevent some in-flight transmission events but seems to be insufficient to prevent superspreading events. They conclude that the risk for on-board transmission of SARS-CoV-2 during long flights is real and has the potential to cause COVID-19 clusters of substantial size, even in business class-like settings with spacious seating arrangements well beyond the established distance used to define close contact on airplanes. (Note that at the time, March 2, the use of face masks was not mandatory on airplanes or at airports, and there was no social distancing on the aircraft.)

Chen J, He H, Cheng W, et al. **Potential transmission of SARS-CoV-2 on a flight from Singapore to Hangzhou, China: An epidemiological investigation.** J Trav Med 2020, Jul 6, 2020. Full-text: <https://doi.org/10.1016/j.tmaid.2020.101816>

Among 335 passengers on a flight from Singapore to Hangzhou in China (a Boeing 787, 5-hour flight, seat occupancy 89%), a total of 16 COVID-19 patients were diagnosed among all passengers, yielding an attack rate of 4.8%. However, after careful investigation, only one case was identified who appears to have become infected during the flight (Chen J 2020). He was seated near four infected passengers from Wuhan for approximately an hour (he had moved a seat) and did not wear his facemask correctly during the flight. The sources of infection in the other 15 passengers were complex and the passengers could have acquired their infections in Wuhan before the tour, or during the group tour before boarding.

Hoehl S, Karaca O, Kohmer M, et al. **Assessment of SARS-CoV-2 Transmission on an International**

Flight and Among a Tourist Group. JAMA Netw Open August 18, 2020, 3(8). Full-text: <https://doi.org/10.1001/jamanetworkopen.2020.18044>

Two likely SARS-CoV-2 transmissions on a 4.5-hour flight from Tel Aviv to Frankfurt, with 7 index cases. Both passengers were seated within two rows of an index case (Hoehl 2020). According to the authors, it could be speculated that the rate may have been reduced further had the passengers worn masks.

Plautz J. **Is it safe to strike up the band in a time of coronavirus?** Science, 17 July 2020. Full-text: <https://www.sciencemag.org/news/2020/07/it-safe-strike-band-time-coronavirus>

Is keeping 2 meters away enough to stay safe from a trumpet at full blast? Try it, find out! Introduce five student musicians – a soprano singer and clarinet, flute, French horn, and trumpet players – in a clean room one at a time and let them perform a short solo piece (Plautz 2020).

Hu M, Lin H, Wang J, et al. **The risk of COVID-19 transmission in train passengers: an epidemiological and modelling study.** Clin Infect Dis 2020, published 29 July. Full-text: <https://doi.org/10.1093/cid/ciaa1057>

How risky is train traveling in the COVID-19 era? To answer this question, analyze passengers in [Chinese high-speed trains](#). Jinfeng Wang and colleagues quantified the transmission risk using data from 2,334 index patients and 72,093 close contacts who had co-travel times of 0–8 hours from 19 December 2019 through 6 March 2020. Unsurprisingly, travelers adjacent to an index patient had the highest attack rate (3.5%) and the attack rate **decreased** with increasing distance, but **increased** with increasing co-travel time. The overall attack rate of passengers with close contact with index patients was 0.32% ([Hu M 2020](#)). The author's conclusion: during COVID outbreaks, when travelling on public transportation in confined spaces such as trains, increase seat distance and reduce passenger density.

Shen Y, Li C, Dong H. **Community Outbreak Investigation of SARS-CoV-2 Transmission Among Bus Riders in Eastern China**. JAMA Intern Med, September 1, 2020. Full-text: <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2770172>

If you take the bus, choose seats near a window (and open it). On January 19, 2020, 68 individuals (including the source patient) took a bus on a 100-minute round trip to attend a worship event. In total, 24 (35%) received a diagnosis of COVID-19 after the event. The authors were able to identify seats for each passenger and divided bus seats into high-risk and low-risk zones ([Shen Y 2020](#)). Passengers in the high-risk zones had moderately but non-significantly higher risk of getting COVID-19 than those in the low-risk zones. On the 3-seat side of the bus, except for the passenger sitting next to the index patient, none of the passengers sitting in seats close to the bus window developed infection. In addition, the driver and passengers sitting close to the bus door also did not develop infection, and only 1 passenger sitting by an operable window developed infection. The absence of a significantly increased risk in the part of the bus closer to the index case suggested that airborne spread of the virus may at least partially explain the markedly high attack rate observed.

Luo K, Lei Z, Hai Z, et al. **Transmission of SARS-CoV-2 in Public Transportation Vehicles: A Case Study in Hunan Province, China**. Open Forum Infectious Diseases 13 September 2020, ofaa430. Full-text: <https://doi.org/10.1093/ofid/ofaa430>

Transmission in a bus. The tour coach was 11.3 meters long and 2.5 meters wide with 49 seats, fully occupied with all windows closed and the ventilation system on during the 2.5-hour trip. Among the 49 passengers (including the driver) who shared the ride with the index person, eight tested positive and eight developed symptoms ([Luo K 2020](#)). The index person sat in the second-to-last row, and the infected passengers were distributed over the middle and rear rows.

Fisher KA, Tenforde MW, Feldstein LR, et al. **Community and Close Contact Exposures Associated with COVID-19 Among Symptomatic Adults ≥18 Years in 11 Outpatient Health Care Facilities — United States, July 2020**. MMWR Morb Mortal Wkly Rep 2020;69:1258–1264. Full-text: <http://dx.doi.org/10.15585/mmwr.mm6936a5>

Eating and drinking and socializing? Everything may well return to normal in about two years. In the meantime, note that adults with a positive SARS-CoV-2 test result

were found to be twice as likely to have had dinner at a restaurant than those with negative test results (Fisher 2020). Kiva Fisher and colleagues conclude that eating and drinking on-site at locations that offer such options might be important risk factors associated with SARS-CoV-2 infection. Bars and restaurants are in for a rough autumn and winter season.

Riediker M, Tsai D. **Estimation of Viral Aerosol Emissions From Simulated Individuals With Asymptomatic to Moderate Coronavirus Disease 2019.** JAMA Netw Open 2020;3(7):e2013807. Full-text: <https://doi.org/10.1001/jamanetworkopen.2020.13807>

In this modeling study, Michael Riediker from the Swiss Centre for Occupational and Environmental Health in Winterthur and Dai-Hua Tsai from the University Hospital of Psychiatry in Zurich, Switzerland, it is estimated that viral load concentrations in a room with an individual who was coughing frequently were very high, with a maximum of 7.44 million copies/m³ from an individual who was a high emitter (Riediker 2020). However, regular breathing from an individual who was a high emitter was modeled to result in lower room concentrations of up to 1248 copies/m³. They conclude that the estimated infectious risk posed by a person with typical viral load who breathes normally was low and that only a few people with very high viral load posed an infection risk in the poorly ventilated closed environment simulated in this study.

In late March 2020, a large outbreak on the aircraft carrier USS Theodore Roosevelt was characterized by widespread transmission with relatively mild symptoms and asymptomatic infection among mostly young, healthy adults with close, congregate exposures. One fifth of infected participants reported no symptoms. Preventive measures, such as using face-coverings and observing social distancing, reduced risk for infection: among 382 service members, those who reported taking preventive measures had a lower infection rate than did those who did not report taking these measures (e.g., wearing a face-covering, 56% versus 81%; avoiding common areas, 54% versus 68%; and observing social distancing, 55% versus 70%, respectively) (Payne 2020).

Adam DC, Wu P, Wong JY, et al. **Clustering and superspreading potential of SARS-CoV-2 infections in Hong Kong.** Nat Med (2020). Full-text: <https://doi.org/10.1038/s41591-020-1092-0>

Dillon Adam, Peng Wu and colleagues identified 4–7 superspreading events (SSEs) across 51 clusters (n = 309 cases) and estimate that 19% (95% confidence interval, 15–24%) of cases seeded 80% of all local transmissions (Adam 2020). After controlling for age, transmission in social settings was associated with more secondary cases than households when controlling for age. Social settings are likely to become major battle grounds of coming SARS-CoV-2 waves.

Wang L, Didelot X, Yang J, et al. **Inference of person-to-person transmission of COVID-19 reveals hidden super-spreading events during the early outbreak phase.** Nat Commun 11, 5006 (2020). Full-text: <https://doi.org/10.1038/s41467-020-18836-4>

Super-spreading events are an important phenomenon in the transmission of many diseases (such as SARS-CoV-1, MERS-CoV, Ebola virus, etc.), in which certain individuals infect a disproportionately large number of people. Here Yuhai Bi, Liang Wang and colleagues show that super-spreading events played an important role in the early stage of the COVID-19 outbreak. They estimated the *dispersion parameter* to be 0.23 (95% CI: 0.13–0.39) (Wang L 2020). (What is the dispersion parameter? Check this FT article: [To beat Covid-19, find today's superspreading 'Typhoid Marys'](#))

Tufekci Z. **This Overlooked Variable Is the Key to the Pandemic.** The Atlantic 2020, published 30 September. Full-text: <https://www.theatlantic.com/health/archive/2020/09/k-overlooked-variable-driving-pandemic/616548/>

Even non-scientists have heard about R_0 (pronounced as “r-naught”)—the basic reproductive number of a pathogen, a measure of its contagiousness on average. But even some scientists may have not yet encountered k , the measure of its dispersion. If you haven’t done it before, do it now: explore k . It’s simply a way of asking whether a virus spreads in a steady manner or in big bursts, whereby one person infects many, all at once (Tufekci 2020).

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3. Prevention

Stefano Lazzari

Introduction

In the absence of an effective vaccine or antiviral treatment, prevention through public health measures remains the mainstay of SARS-COV-2 infection control and pandemic impact mitigation. Effective preventive measures for respiratory infections have been standard practices for many years. However, uncertainties still exist about the role and importance of different transmission routes in the spread of SARS-COV-2 (see chapter *Transmission*). This complicates the choices in terms of the most efficient and effective mix of personal and public health measures to be implemented and the prevention messages to be communicated to the public.

The basic COVID-19 preventive strategies include: the identification and isolation of infectious cases and quarantine for suspected cases and close contacts; changes in individual behaviors including physical and social distancing, use of face masks and hand hygiene; public health measures like travel restrictions, bans on mass gatherings and localized or nationwide lockdowns when the other measures prove ineffective in halting the spread of the virus. Specific prevention measures can be simple recommendations left to the decision of the individual, or mandatory measures to be implemented under control by the public health authorities. Preventive measures can therefore be applied at the personal, community and societal level.

In this chapter we will review the available scientific evidence on the effectiveness of these measures in reducing the spread of SARS-COV-2.

Prevention at the personal level

Good respiratory hygiene/cough etiquette.

Good respiratory hygiene refers to measures aimed at containing respiratory secretions and reducing their spread in the environment or to other people. (Chavis, 2019) Traditionally, they include:

- Covering your mouth and nose with a tissue or with your elbow when coughing or sneezing; and safe disposal of the tissue once used.
- Use of a surgical or tissue face mask.
- Perform hand hygiene often, and always after contact with potentially contaminated objects/materials.

Good respiratory hygiene and cough etiquette are usually recommended for individuals with signs and symptoms of a respiratory infection. However, given the established risk of SARS-COV-2 infection from asymptomatic individuals, public health authorities all over the world have recommended these measures for everybody when in public places. This is not without controversy, in particular on the use of masks in the absence of symptoms.

Face masks

The use of face masks to reduce the risk of infection is an established medical and nursing procedure. It is therefore surprising that it has created such a debate in the context of COVID-19. The initial recommendation by WHO and other health authorities that masks should only be used by health workers and symptomatic patients resulted in controversy among the experts and widespread confusion among the public. This advice was contradictory with the images of people wearing masks in all settings from countries in Asia that successfully managed to contain the pandemic. In addition, the existence of different types of masks greatly complicated communication efforts.

Face masks can prevent transmission of respiratory viruses in two ways:

1. when worn by healthy individuals they are protecting them from infection by reducing the exposure of the mouth and nose to viral particles present in the air or on contaminated hands;
2. when worn by an infected person they perform source control, by reducing the amount of virus dispersed in the environment while coughing, sneezing or talking.

Different types of masks perform these tasks differently, which also dictates the situations in which they should be used. Type of masks most currently used include:

- **N95 (or FFP2) masks**, designed to block 95% of very small particles. They reduce the wearer's exposure to particles including aerosols and large droplets. They also reduce the patient or other bystanders' exposure to particles emitted by the wearer (unless they are equipped with a one-way valve to facilitate breathing).
- **Surgical masks** only filter effectively large particles. Being loose fitted, they will reduce only marginally the exposure of the wearer to droplets and aerosols. They do, however, limit considerably the emission of saliva or droplets by the wearer, reducing the risk of infecting other people.

- **Cloth masks** will stop droplets that are released when the wearer talks, sneezes, or coughs. As recommended by WHO, they should include multi-layers of fabric. When surgical or N95 masks are not available, cloth masks can still reduce the risk of SARS-CoV-2 transmission in public places.

If masks are protective, why they were not widely recommended at the beginning of the pandemic? Whether due to poor communication, fear of shortage of essential medical supplies, or under-appreciation of the role of asymptomatic carriers in spreading the virus, the initial reluctance in promoting mask use and the resulting controversy was clearly not helpful in combating the pandemic and contributed to a general undermining of the credibility of public health authorities.

It was only on 5 June, months into the pandemic, that [WHO released updated guidance on the use of masks](#), recognizing the role that face masks can play in reducing transmission from asymptomatic carriers in particular settings. This was a few days after the publication of a comprehensive review and meta-analysis of observational studies showing a significant reduction in risk of infection with all types of masks ([Chu 2020](#)). Surgical masks were also shown to work in a hamster model ([Chan JF 2020](#)). Other authors, based on reviews or modelling, recommend wearing suitable masks whenever an infected persons may be nearby ([Meselson 2020](#), [Prather 2020](#), [Zhang 2020](#)). (See also the discussion on droplets and aerosol, page 95.)

While there is now a general acceptance, some controversy on the use of masks continues, including on the potential negative effects of wearing masks on health, for example on cardiopulmonary capacity ([Fikenzer, 2020](#)). Regardless of the controversy and the mounting “No-Mask” movements, face masks are clearly “here to stay”. The view of people wearing face masks in public, which in the past surprised and at times amused Western travelers to Asian countries, will be a common sight worldwide for months and maybe for years to come.

Hand Hygiene

The role of fomites in transmission of SARS-CoV-2 remains unclear but cannot be excluded. (Although objects can be easily contaminated by infected droplets and contaminate hands, it is extremely challenging to prove such transmission.) In any case, frequent handwashing is known to disrupt the transmission of respiratory diseases since people routinely make finger-to-nose or finger-to-eye contact ([Kwok, 2015](#)). Handwashing for 30 seconds with ordinary soap is always recommended when there is a contact with a potentially infected item and regularly whenever possible (ex. when returning

home). If water and soap are not available (ex. in public places), use of hydroalcoholic solutions or gel is recommended. These solutions have been shown to efficiently inactivate the SARS-COV-2 virus in 30 seconds (Kratzel, 2020) and can be home-made using a [WHO recommended formulation](#). Hand-hygiene has the added advantage of preventing infections from many other respiratory pathogens. Unfortunately, both water for handwashing and hydroalcoholic solutions are often not available in resource-poor settings (Schmidt, 2020)

Physical/Social distancing and avoiding crowded conditions

Physical distancing means keeping a safe distance from others. The term is often confused with the more common “**social distancing**”, usually imposed during lockdowns, that means reducing social contacts as much as possible by staying home and keeping away from others to prevent the spread of COVID-19.

Social distancing has been unequivocally shown to contribute to reducing the spread of SARS-CoV-2. In Wuhan and Shanghai, daily contacts were reduced 7-8-fold during the social distancing period, with most interactions restricted to the household (Zhang J 2020b, Du Z 2020). Social distancing can be an individual choice, but it is usually imposed by health authorities during “Lockdowns” or “stay-at-home orders”. We will expand on the issues related to lockdowns and social distancing in the sections below.

With the end of lockdowns and the restart of economic and social activities, physical distancing in public places should become an important behavioural aspect of everyday life and an essential measure to reduce the spread of SARS-COV-2. Keeping a safe distance from others seems like a straightforward recommendation but defining what can be considered a “safe distance” is in fact quite complex. In a published meta-analysis (Chu, 2020), the authors estimated that the risk of being infected with SARS-COV-2 is reduced to 13% for those standing at 1 m and further reduced to only 3% beyond that distance. Based on this evidence, the [WHO](#) and [ECDC](#) recommend a minimum interpersonal distance of 1 m, although other agencies and countries suggest 1.5 m (Australia, Italy, Germany), 1.8 m (US CDC), or even 2 meters (Canada, China, UK). (BBC News, 2020)

Some authors suggest that even 2 meters might not be sufficient and that being “safe” would depend on multiple factors related to both the individual and the environment. These could include infecting viral load, duration of exposure, number of individuals present, indoor versus outdoor settings, level of ventilation, and whether face coverings are worn or not. (Qureshi 2020, Jones 2020). In crowded conditions, including public transport (e.g. trains,

buses, metros), physical distancing is often impossible and the use of a protective mask is usually mandatory.

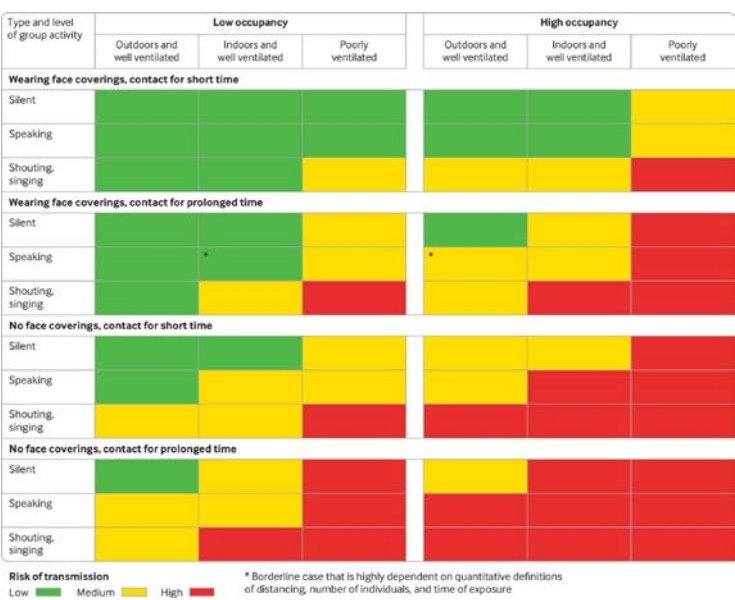


Figure 1. Jones NR,et al. Two metres or one: what is the evidence for physical distancing in covid-19? BMJ. 2020 Aug 25;370:m3223. Reproduced with permission.

Speak quietly, don't shout (or sing)!

Traditionally, visible droplets produced during coughing and sneezing are considered the main carriers of respiratory viruses. It has only recently emerged that normal speech also yields large quantities of particles that are too small to be visible but are large enough to carry a variety of communicable respiratory pathogens and can remain airborne for longer periods. The rate of particle emission during normal human speech is positively correlated with the loudness (amplitude) of vocalization, ranging from approximately 1 to 50 particles per second (0.06 to 3 particles per cm³), regardless of the language spoken (English, Spanish, Mandarin, or Arabic) (Asadi 2019). However, a small fraction of individuals behaves as “speech superemitters,” consistently releasing many more particles than their peers.

These data may help explain the occurrence of some super-spreaders events (e.g. choirs, parties and festivals, slaughterhouses, sport events, religious celebrations, family gatherings, etc.) that are disproportionately responsible for outbreaks of COVID-19 (See Epidemiology section). While research will con-

tinue to study super-spreaders events, people should abide to a very simple rule: **Regardless of physical distance, speak quietly, don't shout!**

Household hygiene

Several studies suggest the possibility of aerosol and fomite transmission of SARS-CoV-2, since the virus can remain viable and infectious in aerosols for hours and on surfaces up to several days (Doremalen 2020, Chin 2020). Though transmission of SARS-COV-2 from contaminated surfaces has not been clearly documented, traditional good home hygiene measures like cleaning floors and furniture, keeping good ventilation and the general disinfection of frequently used objects (e.g. door and window handles, kitchen and food preparation areas, bathroom surfaces, toilets and taps, touchscreen personal devices, computer keyboards, and work surfaces) are recommended to prevent transmission, particularly where confirmed or suspected COVID-19 cases are present (CDC 2020, WHO 20200515).

SARS-COV-2 is sensitive to ultraviolet rays and heat (Chin 2020). Sustained heat at 56°C for 30 minutes, 75% alcohol, chlorine-containing disinfectants, hydrogen peroxide disinfectants and chloroform can effectively inactivate the virus. Common detergents and sodium hypochlorite (bleach) can also be used effectively (Kampf 2020). To avoid poisoning, disinfectants should always be used at the recommended concentrations, wearing appropriate PPE and should never be mixed. US CDC reported a substantial increase in calls to the poison centers in March 2020 associated with improper use of cleaners and disinfectants; many cases were in children <5 years old (MMWR 2020).

Chemoprophylaxis (not there yet!)

In the future, antiviral drugs may be used to reduce viral shedding in suspected cases and as a prophylactic treatment of contacts. As for now, unfortunately, no such drugs are available.

Prevention at the community/societal levels

Widespread testing, quarantine, and intensive contact tracing

Tedros Adhanom Ghebreyesus didn't get everything right in the SARS-CoV-2 pandemic, but he was right when he recommended: "Test! Test! test!" (WHO, 16 March 2020). Indeed, identification, and testing of suspected cases, isolation and care for those confirmed, and tracing, testing and quarantine of close contacts are **critical activities** to try to break the chain of transmission in any epidemic. They worked well, for example, in responding to the 2003 SARS outbreak and many countries in Asia successfully applied them to

COVID-19 (Li 2020, Lam 2020, Park 2020). The South Korea experience has been nicely summarized in an article in [The Guardian](#).

However, despite the [early availability of sensitive PCR tests](#) (Sheridan 2020), many countries in Europe and elsewhere were initially caught by surprise. Unprepared, they struggled at first to provide sufficient testing, isolation and contact tracing capacities to keep up with the pace of spread of SARS-COV-2. In Italy, the lack of laboratory capacities led to limiting PCR tests to symptomatic patients only, missing many asymptomatic cases. Other countries, like Germany, fared better in diagnostics but implementing contact tracing proved difficult everywhere when the epidemic reached its peak, due to the large number of potential contacts of asymptomatic cases and their relatively long incubation period.

Ensuring sufficient testing capacities paired with the development of new rapid diagnostic tests (see section on Diagnosis) will continue to be an essential measure in facing COVID-19 clusters or the “second wave” of infections. Advanced pooled testing strategies (Mallapaty, 2020) and [the use of saliva samples](#) could facilitate the task by allowing the rapid testing of large number of people, as China has done by [testing all the population of large urban areas like Wuhan](#) (more than 10 million people) in less than 2 weeks.

Isolation (separation of ill or infected persons from others) and **quarantine** (the restriction of activities or separation of persons who are not ill, but who may be exposed to an infectious agent or disease) are essential measures to reduce the spread of COVID-19. Unless a patient is hospitalized, quarantine and isolation are usually done at home or in dedicated facilities like hotels, dormitories, or group isolation facilities. (CDC 2020) Given the uncertainty about the infectivity of the suspected individual, preventive measures are similar for both isolation of confirmed cases and quarantine of contacts. Basically, you are required to stay at home or in the facility and avoid non-essential contacts with others, including household members, for a set period to avoid spreading the infection.

The long incubation and high pre-symptomatic infectivity of COVID-19 puts family members of infected individuals at particular risk (Little 2020). The infection rate found for household members varies between 11% and 32% (Bi Q 2020, Wu J 2020). These differences are probably due to different isolation measures implemented inside the family homes. Ideally, people in isolation should have access to a separate bedroom (and bathroom), personal protection equipment (PPE) and should not have contacts with people at high risk of serious COVID-19 disease.

The period of isolation and quarantine required before suspected or confirmed cases can be considered no more infectious is still being debated. Initially, the requirement for a confirmed case was to have clinically recovered and to have two negative RT-PCR results on sequential samples taken at least 24 hours apart. (WHO 2020) This second criteria proved challenging in countries with limited testing capacities and even when tests are available, some patients can continue to have positive PCR results for weeks or months after the cessation of symptoms, leading to prolonged, probably unnecessary isolation periods.

Updated WHO criteria were published in June (WHO 20200617). Based on data showing the rarity of the presence of viral virus after 9 days from symptom onset (Cevic 2020), the new recommendation is to limit the isolation period to:

- 10 days after symptom onset, plus at least 3 additional days without symptoms for symptomatic patients.
- 10 days after positive test for SARS-CoV-2 for asymptomatic cases.

However, several countries, (e.g. Italy), continue to apply the earlier testing criteria including a negative PCR test, which can result in individual being kept in isolation for a longer period.

Recommended quarantine period for contacts and for travelers has not changed and remains set at 14 days, though several countries have reduced it to 10 days (e.g. Switzerland).

Contact tracing can be effective in reducing the risk of spread of the virus (Keeling 2020) but it is a complex and resource intensive exercise. It is most effective when implemented early in the outbreak, **before there is sustained community transmission**. Once cases are soaring, identifying and monitoring all the potential contacts using only the public health resources becomes close to impossible and additional measures like physical distancing, face masks and localized lockdowns become necessary (Cheng 2020). WHO has published detailed **guidance on contact tracing for COVID-19** and alternative approaches to contact tracing that results in resource-saving measures have recently been suggested. (ECDC, April 2020)

As stated by several authors, (Steinbrook, 2020, Salathé 2020) in countries that have managed to bring the pandemic under control a necessary step in “reopening” society was to have sufficient testing and contact tracing capacities to successfully contain the outbreaks that will inevitably occur as social restrictions are removed or relaxed. The coming winter months will show which countries will have learned this important lesson.

Tracking apps

Mobile phone data reveal astonishing details about population movements. According to an analysis by Orange, a French phone operator, data from its telephone subscribers revealed that 17% of the inhabitants of Grand Paris ([Métropole du Grand Paris](#), 7 million people) left the region between March 13 and 20 – just before and after the implementation of the French lockdown measures ([Le Monde](#), 4 April 2020). Again, mobile phone data from individuals leaving or transiting through the prefecture of Wuhan between 1 January and 24 January 2020 showed that the distribution of population outflow from Wuhan accurately predicted the relative frequency and geographical distribution of SARS-CoV-2 infections throughout China until 19 February 2020 ([Jia JS 2020](#)).

Numerous countries have tried to harness the power of the smartphone to design and target measures to contain the spread of the pandemic ([Oliver 2020](#)). In addition to the dissemination of COVID-19 information and prevention messages, the use of smartphones in support to contact tracing has been promoted widely. This contact tracing system (better named “exposure notification”) would basically use an application to detect if the phone has come in close distance for a set period of time from another phone of a person diagnosed with SARS-CoV-2 and therefore potentially infectious. It will then give a warning message prompting the owner to seek medical assistance, self-isolation, and testing.

[The deployment of these tracking applications has faced several hurdles](#), including the need for inter-operability across platforms (Google, Apple) and across countries (unfortunately, each European country has developed its own app); the possibility of false-positive alerts; and the need for a majority of the population to download and regularly activate the app to be truly effective. The need to preserve the privacy of the users forced less performing technical solutions (e.g. decentralized data systems with data only stored in each phone vs centralized database; preference for less-accurate Bluetooth connection over GPS geo-localization; voluntary decision required on the sharing of data; ensuring time-limited storage of collected data, etc.) For example, in June, [Norway's health authority had to delete all data gathered via its Covid-19 contact-tracing app](#) and suspend its further use following a ruling by the Norwegian Data Protection Authority.

A few months into their introductions, most COVID-19 tracking apps have failed to deliver as expected. In almost all countries only a small proportion of the population have downloaded the app (only Qatar, Israel, Australia, Switzerland, and Turkey have seen [downloads above the minimum threshold of 15% of the population](#)) and probably even less people are regularly activat-

ing it. More importantly, the success of a tracking application should not be measured by the number of downloads but by the number of contacts detected, [which so far have been relatively few](#) (due to privacy concerns, the total number of contacts is not available in countries where information is decentralized).

Several countries, including France and Germany, have started to provide additional services with the app, including for accessing laboratory services and receiving test results. Maybe, with these improvements, these tracking applications will become more efficient and their use will increase in future, though they will probably only be only a support rather than a replacement for a traditional “manual” contact tracing system.

Mandatory use of face masks

Wearing a face mask to protect self and others from SARS-COV-2 infection may be an individual choice (see above). However, as of 6 May 2020, [more than 150 countries](#) have made wearing a mask in some settings a mandatory requirement as a collective preventive public health measure. Mandatory settings range from “everywhere in public” to all indoor public places, public transportation, shops, workplaces, schools, etc. Children and people with breathing difficulties are often exempted from the mandatory use of face masks. (US CDC 2020, WHO 2020, ECDC 2020) As a result, the global number of people regularly wearing masks in public has soared, reaching the peak of 80-90% of the population in [most countries in Asia but also in Italy, France, and Spain](#). Surprisingly, mask acceptance has increased to the point of being branded as a [fashion items](#).

As shown in the chart, authorities in Asia have mandated the use of face masks in public at the early stages of the pandemic, which contributed to reduced spread and the sharp drops in infections. As mentioned earlier, in many other parts of the world, conflicting advice with misleading or incomplete information about the usefulness of masks has caused confusion among the population and a late adoption of this preventive measure. In addition, a growing “[no-Masks](#)” movement has gathered momentum, staging rallies in several countries. Regardless, as new infections have started to increase again following the summer reopening, mandatory mask requirements have been introduced again in most European countries and is becoming a norm in most public places.

YouGov COVID-19 behaviour changes tracker: ☰ Wearing a face mask when in public places

% of people in each market who say they are: Wearing a face mask when in public places.

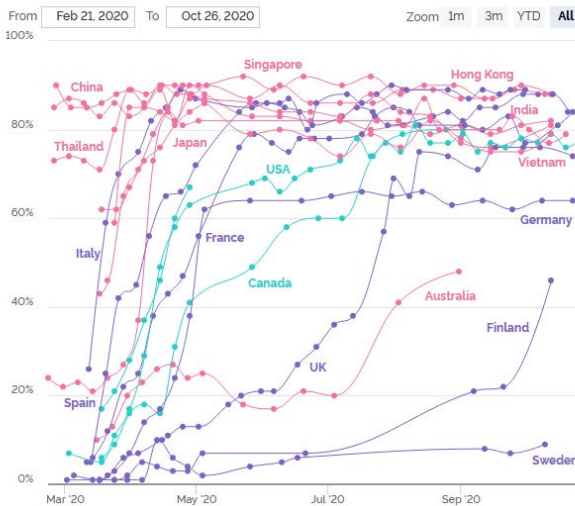


Figure 2. Source: [YouGov.com](https://www.yougov.com). Reproduced with permission.

Ban on mass gatherings

Recognizing their potential role in generating explosive clusters of SARS-COV-2 infections, (McCloskey 2020, Ebrahim 2020) most countries have implemented nationwide bans of mass gathering like sporting and cultural events, concerts, religious celebrations, rallies and political demonstrations, etc. Several important international mass gatherings events have been cancelled or postponed in 2020, including the Tokyo Olympic Games, Euro football championship, Formula 1 Grand Prix races, the Eurovision Song Contest, Geneva Motor Show, Christian Holy Week events in Rome, Umrah pilgrimage to Mecca, and many others.

It is currently uncertain under which conditions cultural events that require closeness of spectators (e.g. cinema, theatre, opera, etc.), religious ceremonies, political rallies, and other social events that require the contemporaneous presence of large numbers of clients in a restricted, closed space (discos, bar, etc.) can be resumed without the risk of resulting in a super spreader event. The limited reopening of these premises during the summer holidays has recently been associated with a resurgence of the spread of the virus observed in Greece, Spain, France, and Italy. Most sport events have resumed,

but without public. WHO has recently published [key recommendations for mass gatherings in the context of COVID-19](#). Unless the risk of SARS-COV-2 spread is reduced significantly, postponing or cancelling of planned large event is likely to continue in the months to come.

Localized and nationwide Lockdowns

Lockdowns (or “stay-at-home orders”) are restrictions of movements of the whole population, ordered by a government authority to suppress or mitigate an epidemic or pandemic. They differ from quarantine in that all residents are supposed to stay at home, except for those involved in essential tasks, while quarantine is usually limited to people suspected to be infected.

Lockdowns and social distancing have been used for centuries in the fight against epidemics, as famously illustrated in the *Decameron*, a book by Boccaccio, an Italian writer, which contains tales told by a group of young people sheltering in a villa outside Florence to escape the Black Death of 1348. However, the 2020 nationwide lockdowns which ordered [almost 4 billion people in 90 countries](#) to stay at home were unprecedented in human history. (see also Chronology) For the first time, lockdowns were imposed initially in a whole city of 10 million people (Wuhan), then to 60 million people in the whole province of Hubei, finally to a whole country (Italy, followed by most other European countries.) Though countries opted for more (China) or less (Europe) strict confinement measures, lockdowns were clearly effective in decreasing a hypothesized infection rate of 60% to 70% to less than 10%. (Cowling 2020)

How strict such measures can be has been shown in Hong Kong (Normile 2020). The recipe: hospitalize all those who test positive, regardless of whether they have symptoms, order two weeks of self-quarantine to all close contacts, introduce electronic wristbands, etc. A website even displays the location of infected people in Hong Kong at all times: <https://chp-dashboard.geodata.gov.hk/covid-19/en.html>. Such strict measures can be very effective but would not be acceptable or feasible in most countries. Indeed, one of the limitations of lockdowns is that they can never be 100% complete. People occupied in essential services (e.g. health, security, transport, communication, food production and delivery, etc.) will need to be allowed to move and work, and sick people will need to continue to access health services.

Generalized lockdowns are blunt prevention tools, affecting the whole healthy population to reduce the risk of transmission from the relatively few potentially infectious individuals. (Hsiang 2020) They impose a major eco-

nomic and social burden on the affected populations, while also preventing at times access to prevention and treatment for other health conditions (Charlesworth 2020). They have been described as a type of “induced coma” for the whole society and economy, though few benefits are also noted, for example on pollution levels. (UNDP 2020) Various authors (Marshall 2020, Pierce 2020, Williams 2020, Galea 2020) have also emphasized the combined impact of the pandemic, social distancing and closures on the mental health of the population. In addition, implementing generalized lockdowns in low-income countries is particularly difficult. People in the informal economy without social net benefits may be forced to choose between the risk of infection and risking of falling into poverty and hunger. (ILO, 2020)

In fact, widespread testing, isolation and quarantine, combined with population behavioral changes (physical distancing, use of masks, hand hygiene) – that have a less disruptive social and economic impact – have been shown to successfully contain COVID-19 if applied widely and consistently (Cowling 2020). A key metric for their success is whether critical care capacities are exceeded. To avoid this, prolonged or intermittent social distancing may be necessary into 2022 (Kissler 2020).

In summary, the tighter you control the infected individuals and trace and isolate the close contacts, the less restriction you will have to impose on the uninfected. The hope is for countries to learn this lesson and, being better prepared, to be able to avoid in future the need for generalized lockdowns to respond to COVID-19 (and other epidemics). However, the resurgence of COVID-19 in Europe is showing how difficult it is to balance health and economic/social imperatives. Until an effective vaccine becomes available, localized or even generalized temporary lockdowns might continue to be required in the fight against this pandemic.

Travel bans/border closures

It has long been recognized that both land, sea and air travel can be efficient and rapid routes for the international spread of a pandemic virus. (Hufnagel 2004, Hollingsworth 2007) The conditions for restricting movements of people and goods between countries in case of a public health emergency are therefore described in the WHO International Health Regulations adopted by all WHO member states in 2005 (IHR 2005).

As of 18 June 2020, almost all (191) countries have taken some measures that restrict people’s movement since the COVID-19 pandemic began. Measures range from control of entry onto the territory of a State to control of movement within a territory, comprising of partial or total border closures (125 countries) and international flight suspensions (122 countries).

As pointed out by some authors ([Habibi 2020](#)), these measures may be in breach of the IHR 2005, as they do not seem grounded on “scientific principles, scientific evidence, or advice from WHO” as required by IHR. ([WHO 2005](#)) This position is based on several scientific studies that have shown how the imposition of travel bans and border closures can be only partially effective in slowing down the introduction and spread of an epidemic or pandemic virus (like influenza or Ebola) while being potentially damaging and even counterproductive ([Brownstein 2006](#), [Mateus 2014](#), [Poletto 2014](#)).

In fact, [widespread travel restrictions and border closures have not prevented SARS-COV-2 from reaching quickly](#) just about every country on the planet (see section on Epidemiology). Though Italy was the first in Europe to impose a [travel ban on China](#), it was also the first European country to experience a major COVID-19 outbreak. Australia has imposed a total travel ban since 24 March that contributed initially to stop the spread of the virus but did not prevent returning citizens and poorly-trained quarantine guards to break the rules and cause the [ongoing major outbreak in Melbourne](#). One reason why travel bans are usually ineffective is that you cannot prevent everybody from entering a country. Some people (e.g. Citizens, long-term residents, diplomats, air or ship crews, health personnel, sometimes businessmen, etc.) are often exempted and able to travel under national or international agreements. Others (e.g. illegal migrants) can cross borders unofficially.

Some authors have also pointed out how the travel bans and border closures can restrict the movement of vital health equipment and supplies (e.g. medicines, PPEs, testing reagents and equipment) and also essential personnel, particularly needed in countries with limited resources ([Devi 2020](#)). Others suggest that early detection, hand washing, self-isolation, and household quarantine will likely be more effective than travel restrictions at mitigating this pandemic. ([Chinazzi 2020](#))

On the other hand, the [economic damage of travel bans](#) has been substantial. The activities of airlines, airports, travel agents, hotels and resorts has basically come to a halt at the peak of the pandemic. [Eurocontrol](#) has recorded a 90% drop in air passenger in Europe at the end of April; the figure has improved with the reopening of borders but is still at -50% compared to 2019 as of mid-July. In May, the [UN World Tourism Organization](#) (UNWTO) projected the potential economic loss for the tourist industry worldwide at US\$ 910 billion to US\$ 1.2 trillion, with 100-120 million jobs at risk.

Generalized travel bans and border closures can effectively reduce the spread of a pandemic virus but, like generalized lockdowns, are blunt tools, affect a large number of uninfected individuals and can result in an erroneous and dangerous false sense of security in the population and in the authorities. In

most cases, they will eventually end up being breached one way or the other. Their impact on the life of many people, the economy and the trade is substantial and strict screening and quarantine measures for travellers can be as effective in avoiding transmission of the virus by imported cases. Hopefully, as countries will increasingly learn how to deal with the risk of COVID-19 in more efficient and effective ways, international travel will finally be allowed to resume in a safe environment.

Vaccinate for seasonal influenza and (hopefully soon) for COVID-19

Several authors ([Richmond 2020](#), [Jaklevic 2020](#), [Singer 2020](#), [Rubin 2020](#), [Maltezoua 2020](#)) and public health agencies are recommending expanding seasonal flu vaccination in the context of the COVID-19 pandemic. This follows concerns about the potential “double epidemic” of COVID-19 and seasonal flu during the winter months ([Balakrishnan 2020](#), [Gostin 2020](#)). There are indeed many similarities (but also a few important differences) between the two diseases ([Solomon 2020](#), [Zayet 2020](#), [Faury 2020](#)) which may complicate the differential diagnosis for symptomatic patients, e.g. similar transmission routes, similar symptoms for mild cases (except for signs of neurological involvement like anosmia), similar high-risk groups for severe complications and mortality. A “double epidemic” could overburden both primary care services and hospitals, require a major increase in diagnostic capacities, lead to unnecessary isolation and quarantine of influenza cases and even increase stigma and discrimination of anyone presenting with symptoms of a respiratory infection ([Rubin 2020](#)). The possibility of COVID-19 and flu co-infection should also *not* be ruled out ([Kim 2020](#)). Combined SARS-CoV-2 and flu diagnostic tests, as [recently approved by the FDA](#) and being evaluated in some [countries in Europe](#), could be useful in quickly identifying the pathogen(s) involved from a single sample.

Increasing coverage of seasonal influenza vaccination among high-risk groups is a good public health measure on its own, as influenza is estimated to cause close to 10 million hospitalizations and between 294,000 and 518,000 deaths every year ([Paget 2019](#), [CDC-US](#)). It is also an essential measure in the response to COVID-19 to avoid a potential breakdown of health care systems and the related increase in mortality and morbidity. Unfortunately, the normal uptake of flu vaccination in high-risk groups (> 65 years of age) has been largely insufficient, [averaging around 50% in OECD countries](#). Along with efforts to increase coverage in the recommended risk groups, additional measures being suggested include reducing the recommended age for vaccination from 65 to 60 years, universal vaccination of children aged 6 months

to 17 years, mandatory vaccination for all health-care workers, including all workers and visitors of long-term care facilities (Balakrishnan 2020, Gostin 2020, CDC).

However, widespread implementation of these additional measures will not be simple. The usual misguided concerns about the safety of vaccines and more recent social media fake news reports about the possibility of flu vaccine causing COVID-19 will need to be addressed. Reduced healthcare seeking behaviors due to fear of SARS-CoV-2 infection could also be a challenge. In addition, despite efforts by vaccine manufacturers and a major increase in flu vaccine production capacities in the last decade, due in part to preparation for a possible flu pandemic (Rockman 2020), vaccine availability is unlikely to be sufficient to meet such an increase in demand, at least for the coming northern hemisphere flu season in 2020-21.

The definition of the composition of the seasonal flu vaccine is agreed by a WHO advisory group of flu experts based on an analysis of the data generated by the WHO Global Influenza Surveillance and Response System (GISRS). The group reviews the results of flu surveillance, laboratory and clinical studies and makes recommendations on the composition of the influenza vaccine based on the best match with available vaccine viruses. The advisory group meetings are held in February (for the northern hemisphere's seasonal influenza vaccine) and in September (for the southern hemisphere's vaccine) to allow sufficient time (7-9 months) for the production of the required doses of vaccine. (Dunning 2020).

Influenza vaccine effectiveness can vary from season to season depending on the similarity or "match" between the flu vaccine and the flu viruses spreading in the community. During those years when the flu vaccine is not well matched to circulating influenza viruses, effectiveness can be as low as 20%, rising to 60% for the years when there is a good match. However, even less effective influenza vaccines have been shown to reduce considerably the burden of severe cases of influenza, admission to ICUs, and flu-related deaths (Thompson 2018, Ferdinands 2019).

Several recent studies have reported that indicators of influenza activity have been declining substantially in 2020 in both the northern (e.g. in Asia and the US) and the southern hemispheres, including in countries that implemented limited lockdown measures (Soo 2020, Olsen 2020, Itaya 2020). The decreased influenza activity was closely associated with the introduction of interventions to reduce SARS-CoV-2 transmission. (Choe 2020). This is really good news, as the evidence on the effectiveness of public health interventions in slowing the spread of a pandemic virus has been otherwise limited (Fong 2020, Xiao 2020, Ryu 2020). If these findings are confirmed during the coming

winter season in the northern hemisphere, not only this would avoid the danger of a “dual epidemic” but it will also confirm that non-pharmaceutical interventions are essential in the response to future pandemics and could become standard interventions, in addition to vaccination, for reducing the health burden of seasonal influenza and other respiratory infections in high risk groups.

On the down side, the limited detection and isolation of flu viruses by the WHO surveillance system will reduce the availability of updated and robust data for the decision on the composition of the flu vaccine for 2021, raising the danger of a poor match between future influenza vaccines and circulating flu viruses.

→ Lockdowns have all but eliminated flu season in the southern hemisphere

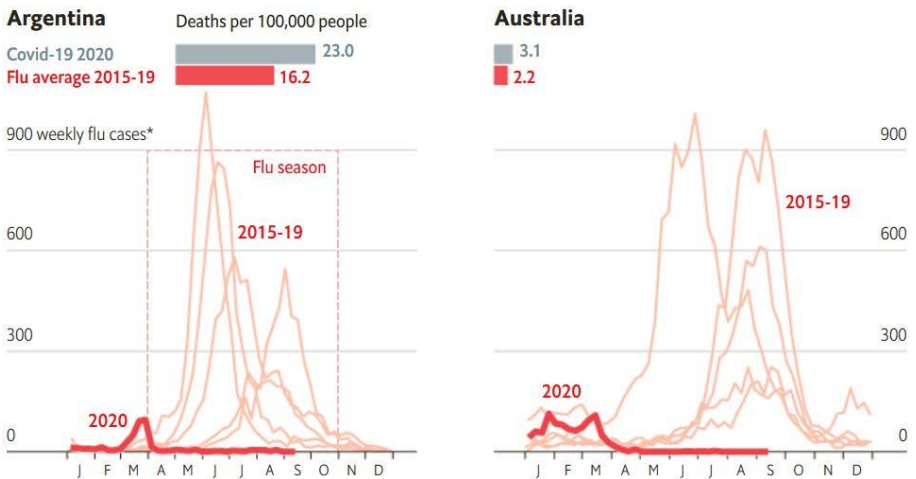


Figure 3. The southern hemisphere skipped flu season in 2020 – Efforts to stop covid-19 have had at least one welcome side-effect. The Economist 2020, published 12 September. Full-text: <https://www.economist.com/graphic-detail/2020/09/12/the-southern-hemisphere-skipped-flu-season-in-2020>. Reproduced with permission.

Additional potential good news could come from research on the effects of influenza vaccination on the severity of SARS-CoV-2 infection. Among the few studies available, a recently pre-published paper (Fink 2020) reports on the analysis of data from 92,664 confirmed COVID-19 cases in Brazil showing that patients who received a trivalent influenza vaccine during the last campaign (March 2020) experienced on average 8% lower odds of needing intensive care treatment (95% CIs [0.86, 0.99]), 18% lower odds of requiring invasive respira-

tory support (0.74, 0.88) and 17% lower odds of death (0.75, 0.89). Similar conclusions were reached in another pre-print paper modelling COVID-19 mortality data and recent influenza vaccination coverage in the US (Zanettini 2020).

More studies are clearly required before reaching conclusions, but the available evidence does suggest that increasing coverage of influenza vaccination would result in both direct and indirect benefits in terms of reduced morbidity and mortality from both COVID-19 and influenza. These efforts could also have long-term benefits in expanding influenza vaccine production and uptake, both for seasonal influenza and in preparation for future flu pandemics.

Experience and lessons learned from these efforts will be of great value once a COVID-19 vaccine becomes available, since production, distribution and promotion of uptake for the new vaccine will face similar challenges and will need to prioritize the same vulnerable populations (Jaklevic 2020, Mendelson 2020).

Containment or mitigation of COVID-19?

Public health interventions to control an outbreak or an epidemic aim at achieving two separate but linked objectives (Zhang 2020, OECD 2020):

- To **contain** the spread by minimizing the risk of transmission from infected to non-infected individuals, eventually **suppressing** transmission and ending the outbreak.
- To **mitigate** the impact by slowing the spread of the disease while protecting those at higher risk. While not halting the outbreak, this would “flatten the epidemic curve”, reduce disease burden and avoid a peak in health care demand. In case of new emerging pathogens, it would also buy time to develop effective treatments or vaccines. (Djidjou-Demasse 2020)

Containment strategies rely heavily on case detection and contact tracing, isolation, and quarantine. They are usually applied most successfully in the early stages of an outbreak or epidemic, when the number of cases is still manageable by the public health system. (Hellewell 2020) When containment measures are insufficient or applied too late, **mitigation** becomes the only option, usually through the imposition of generalized preventive measures like closing of non-essential activities, social distancing, mandatory mask use, or lockdowns. (Parodi 2020, Walker 2020)

During the first months of the COVID-19 pandemic, several countries (China, Vietnam, South Korea, Australia, New Zealand) have shown how the imple-

mentation of a well-timed, comprehensive package of aggressive containment and mitigation policies can be effective in suppressing the COVID-19 epidemic, at least in the short-term. Other countries (most countries in Europe) have not been able to suppress transmission but have managed to mitigate the impact and bring the spread of SARS-CoV-2 down to acceptable levels during the summer months. In others the pandemic is still raging with no end in sight (e.g., US, Brazil, most of Latin America) and a second wave of infections is now becoming evident in several European countries. In any case, as long as the virus is actively spreading anywhere in the world, no country can feel safe (as shown by the recent outbreaks in Victoria, Australia and in New Zealand). The fight against SARS-CoV-2 is far from over.

Conclusion

While the quest for an effective vaccine or antiviral treatment continues, countries are still struggling to find the right mix of preventive measures (and the right balance between health and socio-economic priorities) to build an effective response to the COVID-19 pandemic.

Finding the right prevention mix means identifying what are the most cost-effective measures that can be widely implemented to reduce or halt the transmission of the virus. For this, we need a better understanding of how this virus spreads and how effective the different preventive measures are. Only more research and better science will provide this information.

However, finding the right balance also means recognizing that some measures can be effective, but carry very high social, economic, political, educational, and even health costs. These are political decisions. For example, many European countries have tried very hard to avoid imposing again strict generalized lockdowns, border closures or travel bans. These measures are simply too costly for society to be acceptable.

The best scenario is to be able to respond to new cluster of cases or the acceleration of the spread of the virus, due to “superspreaders” events or a relaxation of individual preventive measures, through localized time-limited public health measures, their effectiveness being judged by better and timely monitoring of the spread of the virus. Even in the absence of COVID-19 vaccines or treatments and comprehensive knowledge of the immune response to SARS-CoV-2, countries can navigate pathways to reduced transmission, decreased severe illness and mortality, and less economic disruption in the short and longer term (Bedford 2020). It is not ideal, it is not being “back to normal”, but in the absence of a “silver bullet” it is probably the best option we have right now to contain this pandemic.

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4. Virology

Emilia Wilson

Wolfgang Preiser

Introduction

In January 2020, a novel virus later named severe acute respiratory syndrome coronavirus (SARS-CoV-2) was isolated from the broncho-alveolar fluid of a patient in Wuhan, People's Republic of China, suffering from what became known as coronavirus disease 2019 (COVID-19). SARS-CoV-2 is highly transmissible and pathogenic. Until present (October 2020), it has infected tens of millions of individuals, causing more than a million deaths and debilitating the economy.

Coronaviruses (CoV) are large, spherical, enveloped RNA viruses with distinct protruding spike glycoproteins visible on the viral surface. The name is derived from the Latin “corona”, which means crown or halo, referencing the characteristic morphology when viewed under an electron microscope (Zuckerman 2009, Perlman 2020). Structural proteins include envelope (E), matrix (M), and nucleocapsid (N). CoV contain a single strand of positive-sense RNA. Their genome size ranges from c. 26 to 32 kilobases, placing them among the known RNA viruses with the largest genomes.

The family *Coronaviridae* belongs to the order Nidovirales, suborder Cornidovirineae. Subfamily Orthocoronavirinae includes four genera: alpha-, beta-, delta- and gammacoronavirus. Genera alpha- and betacoronavirus contain several human-pathogenic subgenera and species. SARS-CoV-2 is a previously unknown betacoronavirus in subgenus Sarbecovirus, like its close relative, severe acute respiratory syndrome-related coronavirus (SARS-CoV). Other notable beta-CoV are Middle East respiratory syndrome-related CoV (MERS-CoV) in subgenus Merbecovirus as well as human CoV HKU1 and human CoV OC43, species Betacoronavirus 1, both in subgenus Embecovirus.

Species in of the family *Coronaviridae* infect various species of animals – humans, other mammals, and birds – causing a broad spectrum of different diseases. Human CoV are primarily respiratory pathogens but may cause enteric disease. Respiratory illness caused by human CoV HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63 is usually mild and “common cold”-like and thus not of major public health concern (Korsman 2012). The highly pathogenic CoV affecting humans cause severe acute respiratory infections often resulting in serious disease and death as was caused by the novel SARS-CoV and

MERS-CoV. There is strong evidence that these viruses emerged recently from animal reservoirs, originating in bats and transmitted to man via intermediate host species. Intra- and inter-species transmission of CoVs, and genetic recombination events contribute to the emergence of new CoV strains.

The following sections will review coronaviruses in general with a more detailed appraisal of the origin, evolution, virological structure and pathogenesis of SARS-CoV-2 to expand knowledge pertaining to COVID-19 and prospective anti-viral and vaccine therapies.

* * *

The complete chapter will be available soon.

* * *

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A consensus statement defining the place of SARS-CoV-2 (provisionally named 2019-nCoV) within the Coronaviridae family.

Ceraolo C, Giorgi FM. **Genomic variance of the 2019-nCoV coronavirus.** J Med Virol. 2020 May;92(5):522-528. PubMed: <https://pubmed.gov/32027036>. Full-text:

<https://doi.org/10.1002/jmv.25700>

Analysis of 56 genomic sequences from distinct patients, showing high sequence similarity (>99%). A few variable genomic regions exist, mainly at the ORF8 locus (coding for accessory proteins).

Zhou P, Yang XL, Wang XG, et al. **A pneumonia outbreak associated with a new coronavirus of probable bat origin.** Nature. 2020 Mar;579(7798):270-273. PubMed:

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Full-length genome sequences from five patients at an early stage of the outbreak, showing 79.6% sequence identity to SARS-CoV and 96% to a bat coronavirus.

Genomic variation

MacLean O, Orton RJ, Singer JB, et al. **No evidence for distinct types in the evolution of SARS-CoV-2.** Virus Evolution. Full-text: <https://doi.org/10.1093/ve/veaa034>

Do not overinterpret genomic data! In this paper, authors discuss the difficulty in demonstrating the existence or nature of a functional effect of a viral mutation, and advise against overinterpretation.

Zhang X, Tan Y, Ling Y, et al. **Viral and host factors related to the clinical outcome of COVID-19.** Nature (2020). Full-text: <https://doi.org/10.1038/s41586-020-2355-0>

Viral variants do not affect outcome. This important study on 326 cases found at least two major lineages with differential exposure history during the early phase of the outbreak in Wuhan. Patients infected with these different clades did not exhibit significant differences in clinical features, mutation rates or transmissibility.

Day T, Gandon S, Lion S, et al. **On the evolutionary epidemiology of SARS-CoV-2.** Curr Biol 2020, June 11. Full-text: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7287426>

Outstanding essay about what little is currently known about the evolution of SARS-CoV-2. At present, there is a lack of compelling evidence that any existing variants impact the progression, severity, or transmission of COVID-19.

Gussow AB, Auslander N, Faure G, Wolf YI, Zhang F, Koonin EV. **Genomic determinants of pathogenicity in SARS-CoV-2 and other human coronaviruses.** Proc Natl Acad Sci U S A. 2020 Jun 30;117(26):15193-15199. PubMed: <https://pubmed.gov/32522874>. Full-text: <https://doi.org/10.1073/pnas.2008176117>

This in-depth molecular analysis reconstructs key genomic features that differentiate SARS-CoV-2 from less pathogenic coronaviruses.

Korber B, Fischer WM, Gnanakaran S, et al. **Tracking changes in SARS-CoV-2 Spike: evidence that D614G increases infectivity of the COVID-19 virus.** Cell July 02, 2020. Full-text: <https://doi.org/10.1016/j.cell.2020.06.043>

A SARS-CoV-2 variant carrying the Spike protein amino acid change D614G (caused by an A-to-G nucleotide mutation at position 23,403 in the Wuhan reference strain) has become the most prevalent form in the global pandemic within a month, indicating a fitness advantage (better transmission).

Plante JA, Liu Y, Liu J, et al. **Spike mutation D614G alters SARS-CoV-2 fitness.** Nature 2020, published 26. October. Full-text: <https://doi.org/10.1038/s41586-020-2895-3>

D614G enhances replication on human lung epithelial cells and primary human airway tissues through an improved infectivity of virions.

Yurkovetskiy L, Wang X, Pascal KE, et al. **Structural and Functional Analysis of the D614G SARS-CoV-2 Spike Protein Variant.** Cell 2020, published 15 September. Full-text: <https://doi.org/10.1016/j.cell.2020.09.032>

D614G is more infectious than the ancestral form on human lung cells, colon cells, and on cells expressing ACE.

Origin and hosts

Andersen KG, Rambaut A, Lipkin WA, Holmes EC, Garry RF. **The proximal origin of SARS-CoV-2.** Nature Medicine. Published: 17 March 2020. Fulltext: <https://www.nature.com/articles/s41591-020-0820-9>

Review on notable genomic features of SARS-CoV-2, compared to alpha- and beta-coronaviruses. Insights on the origin, clearly showing that this virus is not a laboratory construct or a purposefully manipulated virus.

Cui J, Li F, Shi ZL. **Origin and evolution of pathogenic coronaviruses.** Nat Rev Microbiol. 2019 Mar;17(3):181-192. PubMed: <https://pubmed.gov/30531947>. Full-text: <https://doi.org/10.1038/s41579-018-0118-9>

SARS-CoV and MERS-CoV likely originated in bats, both jumping species to infect humans through different intermediate hosts.

Lam TT, Shum MH, Zhu HC, et al. **Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins.** Nature. 2020 Mar 26. PubMed: <https://pubmed.gov/32218527>. Fulltext: <https://doi.org/10.1038/s41586-020-2169-0>

Do Malayan pangolins act as intermediate hosts? Metagenomic sequencing identified pangolin-associated coronaviruses, including one with strong similarity to SARS-CoV-2 in the receptor-binding domain.

Xiao K, Zhai J, Feng Y, et al. **Isolation of SARS-CoV-2-related coronavirus from Malayan pangolins.** Nature. 2020 May 7. PubMed: <https://pubmed.gov/32380510>. Full-text: <https://doi.org/10.1038/s41586-020-2313-x>

In a wildlife rescue center, authors found a coronavirus in 25 Malayan pangolins (some of them were very sick), showing 90-100% amino acid identity with SARS-CoV-2 in different genes. Comparative genomic analysis suggested that SARS-CoV-2 might have originated from the recombination of a Pangolin-CoV-like virus with a Bat-CoV-RaTG13-like virus. As the RBD of Pangolin-CoV is virtually identical to that of SARS-CoV-2, the virus in pangolins presents a potential future threat to public health. Pangolins and bats are both nocturnal animals, eat insects, and share overlapping ecological niches, which make pangolins the ideal intermediate host. *Stop the illegal pangolin trade!*

Zhang T, Wu Q, Zhang Z. **Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak.** Curr Biol. 2020 Mar 13. PubMed: <https://pubmed.gov/32197085>. Fulltext: <https://doi.org/10.1016/j.cub.2020.03.022>

This study suggests that pangolin species are a natural reservoir of SARS-CoV-2-like CoVs. Pangolin-CoV was 91.0% and 90.6% identical to SARS-CoV-2 and Bat-CoV RaTG13, respectively.

Zhou H, Chen X, Hu T, et al. **A Novel Bat Coronavirus Closely Related to SARS-CoV-2 Contains Natural Insertions at the S1/S2 Cleavage Site of the Spike Protein.** Curr Biol. 2020 May 11. PubMed: <https://pubmed.gov/32416074>. Full-text: <https://doi.org/10.1016/j.cub.2020.05.023>

A novel bat-derived coronavirus was identified from a metagenomics analysis of samples from 227 bats collected from Yunnan Province in 2019. Notably, RmYN02 shares 93.3% nucleotide identity with SARS-CoV-2 at the scale of the complete genome and 97.2% identity in the lab gene, in which it is the closest relative of SARS-CoV-2 reported to date. However, RmYN02 showed low sequence identity (61.3%) in the receptor binding domain and might not bind to ACE2.

Stability and transmission of the virus

Chin AW, Chu JT, Perera MR, et al. **Stability of SARS-CoV-2 in different environmental conditions.** The Lancet Microbe 2020, April 02. Full-text: [https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247\(20\)30003-3/fulltext](https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30003-3/fulltext)

SARS-CoV-2 was highly stable at 4°C (almost no reduction on day 14) but sensitive to heat (70°C: inactivation 5 min, 56°: 30 min, 37°: 2 days). It also depends on the surface: No infectious virus could be recovered from print and tissue paper after 3 hours, from treated wood and cloth on day 2, from glass and banknotes on day 4, stainless steel and plastic on day 7. Strikingly, a detectable level of infectious virus (<0.1% of the original inoculum) was still present on the outer layer of a surgical mask on day 7.

Kim YI, Kim SG, Kim SM, et al. **Infection and Rapid Transmission of SARS-CoV-2 in Ferrets.** Cell Host Microbe. 2020 Apr 5. PubMed: <https://pubmed.gov/32259477>. Full-text: <https://doi.org/10.1016/j.chom.2020.03.023>.

Ferrets shed the virus in nasal washes, saliva, urine, and feces up to 8 days post-infection. They may represent an infection and transmission animal model of COVID-19 that may facilitate development of SARS-CoV-2 therapeutics and vaccines.

Leung NH, Chu Dk, Shiu EY. **Respiratory virus shedding in exhaled breath and efficacy of face masks.** Nature Med 2020, April 3. <https://doi.org/10.1038/s41591-020-0843-2>

This study from Hong Kong (performed 2013-16) quantified virus in respiratory droplets and aerosols in exhaled breath. In total, 111 participants (infected with seasonal coronavirus, influenza or rhinovirus) were randomized to wear or not to wear a simple surgical face mask. Results suggested that masks could be used by ill people to reduce onward

transmission. In respiratory droplets, seasonal coronavirus was detected in 3/10 (aerosols: 4/10) samples collected without face masks, but in 0/11 (0/11) from participants wearing face masks. Influenza viruses were detected in 6/23 (8/23) without masks, compared to 1/27 (aerosol 6/27!) with masks. For rhinovirus, there were no significant differences at all. Of note, authors also identified virus in some participants who did not cough at all during the 30 min exhaled breath collection, suggesting droplet and aerosol routes of transmission from individuals with no obvious signs or symptoms.

Shi J, Wen Z, Zhong G, et al. **Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2.** Science. 2020 Apr 8. PubMed: <https://pubmed.gov/32269068>. Full-text: <https://doi.org/10.1126/science.abb7015>

SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks. However, ferrets and cats are permissive to infection and cats were susceptible to airborne infection. But cat owners can relax. Experiments were done in a small number of cats exposed to high doses of the virus, probably more than found in real-life. It also remains unclear if cats secrete enough coronavirus to pass it on to humans.

van Doremalen N, Bushmaker T, Morris DH, et al. **Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1.** N Engl J Med. 2020 Mar 17. PubMed: <https://pubmed.gov/32182409>. Fulltext: <https://doi.org/10.1056/NEJMc2004973>

Stability of SARS-CoV-2 was similar to that of SARS-CoV-1, indicating that differences in the epidemics probably arise from other factors and that aerosol and fomite transmission of SARS-CoV-2 is plausible. The virus can remain viable and infectious in aerosols for hours and on surfaces up to days (depending on the inoculum shed).

Chan KH, Sridhar S, Zhang RR, et al. **Factors affecting stability and infectivity of SARS-CoV-2.** J Hosp Infect. 2020 Jul 8. PubMed: <https://pubmed.gov/32652214>. Full-text: <https://doi.org/10.1016/j.jhin.2020.07.009>

Dry heat is bad, damp cold is good (for the virus). Dried SARS-CoV-2 virus on glass retained viability for over 3-4 days at room temperature and for 14 days at 4°C, but lost viability rapidly at 37°C. SARS-CoV-2 in solution remained viable for much longer under the same different temperature conditions.

Cell tropism, ACE expression

Chu H, Chan JF, Yuen TT, et al. **Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: an observational study.** *Lancet Microbe* April 21, 2020. Full-text: [https://doi.org/10.1016/S2666-5247\(20\)30004-5](https://doi.org/10.1016/S2666-5247(20)30004-5)

An elegant study, explaining distinct clinical features of COVID-19 and SARS. Investigation of cell susceptibility, species tropism, replication kinetics, and virus-induced cell damage from both SARS-CoVs, using live infectious virus particles. SARS-CoV-2 replicated more efficiently in human pulmonary cells, indicating that SARS-CoV-2 has most likely adapted better to humans. SARS-CoV-2 replicated significantly less in intestinal cells (might explain lower diarrhea frequency compared to SARS) but better in neuronal cells, highlighting the potential for neurological manifestations.

Hou YJ, Okuda K, Edwards CE, et al. **SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract.** *Cell*, May 26, 2020. Full-text: <https://doi.org/10.1016/j.cell.2020.05.042>

This study quantitated differences in ACE2 receptor expression and SARS-CoV-2 infectivity in the nose (high) vs the peripheral lung (low). If the nasal cavity is the initial site mediating seeding of the lung via aspiration, these studies argue for the widespread use of masks to prevent aerosol, large droplet, and/or mechanical exposure to the nasal passages.

Hui KPY, Cheung MC, Perera RAPM, et al. **Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures.** *Lancet Respir Med.* 2020 May 7. PubMed: <https://pubmed.gov/32386571>. Full-text: [https://doi.org/10.1016/S2213-2600\(20\)30193-4](https://doi.org/10.1016/S2213-2600(20)30193-4)

More insights into the transmissibility and pathogenesis. Using *ex vivo* cultures, the authors evaluated tissue and cellular tropism of SARS-CoV-2 in human respiratory tract and conjunctiva in comparison with other coronaviruses. In the bronchus and in the conjunctiva, SARS-CoV-2 replication competence was higher than SARS-CoV. In the lung, it was similar to SARS-CoV but lower than MERS-CoV.

Shang J, Ye G, Shi K. **Structural basis of receptor recognition by SARS-CoV-2.** *Nature* 2020, March 30. Full-text: <https://doi.org/10.1038/s41586-020-2179-y>.

How well does SARS-CoV-2 recognize hACE2? Better than other coronaviruses. Compared to SARS-CoV and RaTG13 (isolated from bats), ACE2-binding affinity is higher. Functionally important epitopes in SARS-CoV-2 RBM are described that can potentially be targeted by neutralizing antibody drugs.

Sungnak W, Huang N, Bécavin C, et al. **SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes.** Nature Medicine, Published: 23 April 2020. Full-text: <https://www.nature.com/articles/s41591-020-0868-6>

Another elegant paper, confirming the expression of ACE2 in multiple tissues shown in previous studies, with added information on tissues not previously investigated, including nasal epithelium and cornea and its co-expression with TMPRSS2. Potential tropism was analyzed by surveying expression of viral entry-associated genes in single-cell RNA-sequencing data from multiple tissues from healthy human donors. These transcripts were found in specific respiratory, corneal and intestinal epithelial cells, potentially explaining the high efficiency of SARS-CoV-2 transmission.

Spike protein

Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. **The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade.** Antiviral Res. 2020 Apr;176:104742. PubMed: <https://pubmed.gov/32057769>. Fulltext: <https://doi.org/10.1016/j.antiviral.2020.104742>

Identification of a peculiar furin-like cleavage site in the Spike protein of SARS-CoV-2, lacking in other SARS-like CoVs. Potential implication for the development of antivirals.

Watanabe Y, Allen JD, Wrapp D, McLellan JS, Crispin M. **Site-specific glycan analysis of the SARS-CoV-2 spike.** Science. 2020 May 4. PubMed: <https://pubmed.gov/32366695>. Full-text: <https://doi.org/10.1126/science.abb9983>

The surface of the envelope spike is dominated by host-derived glycans. These glycans facilitate immune evasion by shielding specific epitopes from antibody neutralization. SARS-CoV-2 S gene encodes 22 N-linked glycan sequons per protomer. Using a site-specific mass spectrometric approach, the authors reveal these glycan structures on a recombinant SARS-CoV-2 S immunogen.

Cai Y, Zhang J, Xiao T, et al. **Distinct conformational states of SARS-CoV-2 spike protein.** Science 21 Jul 2020. Full-text: <https://doi.org/10.1126/science.abd4251>

The authors report two cryo-EM structures, derived from a preparation of the full-length S protein, representing its pre-fusion (2.9Å resolution) and post-fusion (3.0Å resolution) conformations, respectively, and identify a structure near the fusion peptide – the fusion peptide proximal region (FPPR), which may play a critical role in the fusogenic structural rearrangements of S protein.

Ke Z, Oton J, Qu K, et al. **Structures and distributions of SARS-CoV-2 spike proteins on intact virions.** Nature 2020, published 17 August. Full-text: <https://doi.org/10.1038/s41586-020-2665-2>

More on how SARS-CoV-2 Spike (S) proteins function and how they interact with the immune system. This work extends the knowledge of the structures, conformations and distributions of S trimers within virions.

Toelzer C, Gupta K, Yadav SK, et al. **Free fatty acid binding pocket in the locked structure of SARS-CoV-2 spike protein.** Science 21 Sep 2020. Full-text: <https://doi.org/10.1126/science.abd3255>

The structure of the SARS-CoV-2 S glycoprotein. The RBDs tightly bind the essential free fatty acid (FFA) linoleic acid (LA) in three composite binding pockets. The LA-binding pocket presents a promising target for future development of small molecule inhibitors that, for example, could irreversibly lock S in the closed conformation and interfere with receptor interactions.

Turoňová B, Sikora M, Schürmann C, et al. **In situ structural analysis of SARS-CoV-2 spike reveals flexibility mediated by three hinges.** Science 2020, published 18 August. Full-text: <https://science.sciencemag.org/content/early/2020/08/17/science.abd5223>

This work shows that the stalk domain of S contains three hinges, allowing S to scan the host cell surface, shielded from antibodies by an extensive glycan coat.

Binding to ACE

Lan J, Ge J, Yu J, et al. **Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor.** Nature. Published: 30 March 2020. Full-text: <https://www.nature.com/articles/s41586-020-2180-5>

To elucidate the SARS-CoV-2 RBD and ACE2 interaction at a higher resolution/atomic level, authors used X-ray crystallography. Binding mode was very similar to SARS-CoV, arguing for a convergent evolution of both viruses. The epitopes of two SARS-CoV antibodies targeting the RBD were also analysed with the SARS-CoV-2 RBD, providing insights into the future identification of cross-reactive antibodies.

Wang Q, Zhang Y, Wu L, et al. **Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2.** Cell. 2020 Apr 7. PubMed: <https://pubmed.gov/32275855>. Full-text: <https://doi.org/10.1016/j.cell.2020.03.045>

Atomic details of the crystal structure of the C-terminal domain of SARS-CoV-2 spike protein in complex with human ACE2 are presented. The hACE2 binding mode of SARS-CoV-2 seems to be similar to SARS-CoV, but some key residue substitutions slightly strengthen the interaction and lead to higher affinity for receptor binding. Antibody experiments indicated notable differences in antigenicity between SARS-CoV and SARS-CoV-2

Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. **Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2**. Science. 2020 Mar 27;367(6485):1444-1448. PubMed:

<https://pubmed.gov/32132184>. Full-text: <https://doi.org/10.1126/science.abb2762>

Using cryo-electron microscopy, this paper shows how SARS-CoV-2 binds to human cells. The first step in viral entry is the binding of the viral trimeric spike protein to the human receptor angiotensin-converting enzyme 2 (ACE2). The authors present the structure of human ACE2 in complex with a membrane protein that it chaperones, B0AT1. The structures provide a basis for the development of therapeutics targeting this crucial interaction.

Starr TN, Greaney AJ, Hilton SK, et al. **Deep mutational scanning of SARS-CoV-2 receptor binding domain reveals constraints on folding and ACE2 binding**. Cell August 11, 2020. Full-text: <https://doi.org/10.1016/j.cell.2020.08.012>

The authors have systematically changed every amino acid in the RBD and determine the effects of the substitutions on Spike expression, folding, and ACE2 binding. The work identifies structurally constrained regions that would be ideal targets for COVID-19 countermeasures and demonstrates that mutations in the virus which enhance ACE2 affinity can be engineered but have not, to date, been naturally selected during the pandemic.

Yang J, Petitjean SJL, Koehler M. **Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor**. Nat Commun 11, 4541 (2020). Full-text: <https://doi.org/10.1038/s41467-020-18319-6>

How the receptor binding domain serves as the binding interface within the S-glycoprotein with the ACE2 receptor. Kinetic and thermodynamic properties of this binding pocket.

Cell entry

Hoffmann M, Kleine-Weber H, Schroeder S, et al. **SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor**. Cell. 2020 Mar 4.

PubMed: <https://pubmed.gov/32142651>. Fulltext:

<https://doi.org/10.1016/j.cell.2020.02.052>

This work shows how viral entry happens. SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming. In addition, sera from convalescent SARS patients cross-neutralized SARS-2-S-driven entry.

Letko M, Marzi A, Munster V. **Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses.** Nat Microbiol. 2020 Apr;5(4):562-569. PubMed: <https://pubmed.gov/32094589>. Full-text: <https://doi.org/10.1038/s41564-020-0688-y>

Important work on viral entry, using a rapid and cost-effective platform which allows to functionally test large groups of viruses for zoonotic potential. Host protease processing during viral entry is a significant barrier for several lineage B viruses. However, bypassing this barrier allows several coronaviruses to enter human cells through an unknown receptor.

Ou X, Liu Y, Lei X, et al. **Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV.** Nat Commun. 2020 Mar 27;11(1):1620. PubMed: <https://pubmed.gov/32221306>. Fulltext: <https://doi.org/10.1038/s41467-020-15562-9>

More on viral entry and on (the limited) cross-neutralization between SARS-CoV and SARS-CoV-2.

Yuan M, Wu NC, Zhu X, et al. **A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV.** Science. 2020 Apr 3. PubMed: <https://pubmed.gov/32245784>. Full-text: <https://doi.org/10.1126/science.abb7269>

Insights into antibody recognition and how SARS-CoV-2 can be targeted by the humoral response, revealing a conserved epitope shared between SARS-CoV and SARS-CoV-2. This epitope could be used for vaccines and the development of cross-protective antibodies.

Zhang L, Lin D, Sun X, et al. **Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved alpha-ketoamide inhibitors.** Science. 2020 Mar 20. PubMed: <https://pubmed.gov/32198291>. Fulltext: <https://doi.org/10.1126/science.abb3405>

Description of the X-ray structures of the main protease (Mpro, 3CLpro) of SARS-CoV-2 which is essential for processing the polyproteins that are translated from the viral RNA. A complex of Mpro and an optimized protease α -ketoamide inhibitor is also described.

Cantuti-Castelvetri L, Ojha R, Pedro LD, et al. **Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity.** Science 2020, published 20 October. Full-text: <https://doi.org/10.1126/science.abd2985>

Neuropilin-1 (NRP1), known to bind furin-cleaved substrates, significantly potentiates SARS-CoV-2 infectivity, an effect blocked by a monoclonal blocking antibody against NRP1.

Daly JL, Simonetti B, Klein K, et al. **Neuropilin-1 is a host factor for SARS-CoV-2 infection.** Science 2020, published 20 October. Full-text: <https://doi.org/10.1126/science.abd3072>

More on how S binds to cell surface neuropilin-1 (NRP1) and neuropilin-2 (NRP2) receptors.

RNA-dependent RNA polymerase (RdRp)

Gao Y, Yan L, Huang Y, et al. **Structure of the RNA-dependent RNA polymerase from COVID-19 virus**. Science. 15 May 2020; Vol. 368, Issue 6492, pp. 779-782. Full-text: <https://doi.org/10.1126/science.abb7498>

Using cryogenic electron microscopy, the authors describe the structure of the RNA-dependent RNA polymerase, another central enzyme of the viral replication machinery. It is also shown how remdesivir and sofosbuvir bind to this polymerase. The authors determined a 2.9-angstrom-resolution structure of the RNA-dependent RNA polymerase (also known as nsp12), which catalyzes the synthesis of viral RNA, in complex with two cofactors, nsp7 and nsp8.

Hillen HS, Kocik G, Farnung L et al. **Structure of replicating SARS-CoV-2 polymerase**. Nature 2020. Full-text: <https://doi.org/10.1038/s41586-020-2368-8>

The cryo-electron microscopic structure of the SARS-CoV-2 RdRp in active form, mimicking the replicating enzyme. Long helical extensions in nsp8 protrude along the exiting RNA, forming positively charged 'sliding poles'. These sliding poles can account for the known processivity of the RdRp that is required for replicating the long coronavirus genome. A nice video provides an animation of the replication machine.

Chen J, Malone B, Llewellyn E, et al. **Structural basis for helicase-polymerase coupling in the SARS-CoV-2 replication-transcription complex**. Cell 2020, 27 July, 2020. Full-text: <https://doi.org/10.1016/j.cell.2020.07.033>

A cryo-electron microscopic structure of the SARS-CoV-2 holo-RdRp with an RNA template-product with two molecules of the nsp13 helicase and identify a new potential target for future antiviral drugs.

Wolff G, Limpnes RW, Zevenhoven-Dobbe JC, et al. **A molecular pore spans the double membrane of the coronavirus replication organelle**. Science 06 Aug 2020; eabd3629. Full-text: <https://doi.org/10.1126/science.abd3629>

Coronavirus replication is associated with virus-induced cytosolic double-membrane vesicles, which may provide a tailored micro-environment for viral RNA synthesis in the infected cell. Visualization of a molecular pore complex that spans both membranes of the double-membrane vesicle and would allow export of RNA to the cytosol. Although the exact mode of function of this molecular pore remains to be elucidated, it would clearly represent a key structure in the viral replication cycle that may offer a specific drug target.

Animals and animal models

Bao L, Deng W, Huang B, et al. **The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice.**

Nature. 2020 May 7. PubMed: <https://pubmed.gov/32380511>. Full-text:

<https://doi.org/10.1038/s41586-020-2312-y>

In transgenic mice bearing human ACE2 and infected with SARS-CoV-2, the pathogenicity of the virus was demonstrated. This mouse model will be valuable for evaluating antiviral therapeutics and vaccines as well as understanding the pathogenesis of COVID-19.

Chan JF, Zhang AJ, Yuan S, et al. **Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility.** Clin Infect Dis. 2020 Mar 26. PubMed:

<https://pubmed.gov/32215622>. Fulltext: <https://doi.org/10.1093/cid/ciaa325>

A readily available hamster model as an important tool for studying transmission, pathogenesis, treatment, and vaccination against SARS-CoV-2.

Chandrashekar A, Liu J, Martinot AJ, et al. **SARS-CoV-2 infection protects against rechallenge**

in rhesus macaques. Science. 2020 May. PubMed: <https://pubmed.gov/32434946>. Full-text:

<https://doi.org/10.1126/science.abc4776>

No re-infection in macaques. Following initial viral clearance, 9 rhesus macaques were re-challenged on day 35 with the same doses of virus that were utilized for the primary infection. Very limited viral RNA was observed in BAL on day 1 after re-challenge, with no viral RNA detected at subsequent timepoints. These data show that SARS-CoV-2 infection induced protective immunity against re-exposure in nonhuman primates.

Halfman PJ, Hatta M, Chiba S, et al. **Transmission of SARS-CoV-2 in Domestic Cats.** NEJM May

13, 2020. Full-text: <https://www.nejm.org/doi/full/10.1056/NEJMc2013400>

Three domestic cats were inoculated with SARS-CoV-2. One day later, an uninfected cat was cohoused with each of the inoculated cats. All six cats became infected and developed antibody titers but none showed any symptoms. Cats may be a silent intermediate host.

Rockx B, Kuiken T, Herfst S, et al. **Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model.** Science 17 Apr 2020. Full text:

<https://science.sciencemag.org/content/early/2020/04/16/science.abb7314>

Macaques may serve as a model to test therapeutic strategies. Virus was excreted from nose and throat in the absence of clinical signs, and was detected in type I and II pneumocytes *in foci* of diffuse alveolar damage and in ciliated epithelial cells of nasal, bronchial, and bronchiolar mucosae. In SARS-CoV infection, lung lesions were typically more severe, while they were milder in MERS-CoV infection, where virus was detected mainly in type II pneumocytes.

Munster VJ, Feldmann F, Williamson BN, et al. **Respiratory disease in rhesus macaques inoculated with SARS-CoV-2.** Nature 2020. Full-text: <https://doi.org/10.1038/s41586-020-2324-7>
SARS-CoV-2 caused respiratory disease in 8 rhesus macaques, lasting 8-16 days. High viral loads were detected in swabs as well as in bronchoalveolar lavages. This “model” recapitulates COVID-19, with regard to virus replication and shedding, the presence of pulmonary infiltrates, histological lesions and seroconversion.

Sia SF, Yan L, Chin AWH. et al. **Pathogenesis and transmission of SARS-CoV-2 in golden hamsters.** Nature 2020. Full-text: <https://doi.org/10.1038/s41586-020-2342-5>
In most cases, you don't need monkeys. Golden Syrian hamsters may also work. SARS-CoV-2 transmitted efficiently from inoculated hamsters to naïve hamsters by direct contact and via aerosols. Transmission via fomites in soiled cages was less efficient. Inoculated and naturally-infected hamsters showed apparent weight loss, and all animals recovered with the detection of neutralizing antibodies.

Sit TH, Brackman CJ, Ip SM et al. **Infection of dogs with SARS-CoV-2.** Nature 2020. Full-text: <https://www.nature.com/articles/s41586-020-2334-5>
Two out of fifteen dogs (one Pomeranian and one German Shepherd) from households with confirmed COVID-19 cases in Hong Kong were found to be infected. Both dogs remained asymptomatic but later developed antibody responses detected using plaque reduction neutralization assays. Genetic analysis suggested that the dogs caught the virus from their owners. It still remains unclear whether infected dogs can transmit the virus to other animals or back to humans.

Dinnon KH, Leist SR, Schäfer A et al. **A mouse-adapted model of SARS-CoV-2 to test COVID-19 countermeasures.** Nature, August 27, 2020. Full-text: <https://doi.org/10.1038/s41586-020-2708-8>
Unfortunately, standard laboratory mice do not support infection with SARS-CoV-2 due to incompatibility of the S protein to the murine ortholog (mACE2) of the human receptor. This work has developed a recombinant virus (SARS-CoV-2 MA) that could utilize mACE2 for entry. This model may be helpful in studying COVID-19 pathogenesis.

Muñoz-Fontela C, Dowling WE, Funnell SGP, et al. **Animal models for COVID-19.** Nature. 2020 Sep 23. PubMed: <https://pubmed.gov/32967005>. Full-text: <https://doi.org/10.1038/s41586-020-2787-6>

Mice, hamsters, ferrets, minks, cats, pigs, fruit bats, monkeys: a variety of murine models for mild and severe COVID-19 have been described or are under development. All will be useful for vaccine and antiviral evalu-

ation and some share features with the human disease. Review (performed by a huge international collaboration).

Vaccine (see also Immunology)

Le TT, Andreadakis Z, Kumar A, et al. **The COVID-19 vaccine development landscape.** Nature reviews drug discovery. 09 April 2020. Full-text: <https://www.nature.com/articles/d41573-020-00073-5>.

Brief data-driven overview by seven experts. The conclusion is that efforts are unprecedented in terms of scale and speed and that there is an indication that vaccine could be available by early 2021. As of 8 April 2020, the global vaccine landscape includes 115 candidates, of which the 5 most advanced candidates have already moved into clinical development, including mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologics, INO-4800 from Inovio, LV-SMENP-DC and pathogen-specific aAPC from Shenzhen Geno-Immune Medical Institute. The race is on!

Callaway E. **The race for coronavirus vaccines: a graphical guide, Eight ways in which scientists hope to provide immunity to SARS-CoV-2.** Nature 2020, 28 April 2020. 580, 576-577. Full-text: <https://doi.org/10.1038/d41586-020-01221-y>

Fantastic graphic review on current vaccine development. Easy to understand, it explains different approaches such as virus, viral-vector, nucleic-acid and protein-based vaccines.

Zhu FC, Li YH, Guan XH. **Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial.** Lancet May 22, 2020. Full-text: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31208-3/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31208-3/fulltext)

Open label Phase I trial of an Ad5 vectored COVID-19 vaccine, using the full-length spike glycoprotein. A total of 108 healthy adults aged between 18 and 60 years from Wuhan, China, were given three different doses. ELISA antibodies and neutralising antibodies increased significantly and peaked 28 days post-vaccination. Specific T cell response peaked at day 14 post-vaccination. Follow up is still short and authors are going to follow up the vaccine recipients for at least 6 months, so more data will be obtained. Of note, adverse events were relatively frequent, encompassing pain at injection sites (54%), fever (46%), fatigue (44%) and headache (39%). Phase II studies are underway.

Pathogenesis

Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. **Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19.** Cell May 15, 2020. Full-text: <https://doi.org/10.1016/j.cell.2020.04.026>

Incredible in-depth analysis of host response to SARS-CoV-2 and other human respiratory viruses in cell lines, primary cell cultures, ferrets, and COVID-19 patients. Data consistently revealed a unique and inappropriate inflammatory response to SARS-CoV-2 which is imbalanced with regard to controlling virus replication versus activation of the adaptive immune response. It is defined by low levels of type I and III interferons juxtaposed to elevated chemokines and high expression of IL-6. The authors propose that reduced innate antiviral defenses coupled with exuberant inflammatory cytokine production are the defining and driving features of COVID-19. Given this dynamic, treatments for COVID-19 have less to do with the IFN response and more to do with controlling inflammation.

Bordoni V, Sacchi A, Cimini E. **An inflammatory profile correlates with decreased frequency of cytotoxic cells in COVID-19.** Clinical Infectious Diseases 2020, May 15. Full-text: <https://doi.org/10.1093/cid/ciaa577>

The increase in inflammatory mediators is correlated with a reduction of innate and adaptive cytotoxic antiviral function. The authors found a lower perforin+ NK cell number in 7 intensive care unit (ICU) patients compared to 41 non-ICU patients, suggesting an impairment of the immune cytotoxic arm as a pathogenic mechanism.

Grifoni A, Weiskopf D, Ramirez SI, et al. **Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals.** Cell 2020. Full-text: <https://doi.org/10.1016/j.cell.2020.05.015>

Cellular response is a major knowledge gap. This important study identified circulating SARS-CoV-2-specific CD8 and CD4 T cells in 70-100% of 20 COVID-19 convalescent patients, respectively. CD4 T cell responses to spike protein were robust and correlated with the magnitude of IgG titers. Of note, the authors detected SARS-CoV-2-reactive CD4 T cells in 40-60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating seasonal coronaviruses and SARS-CoV-2.

Li H, Liu L, Zhang D, et al. **SARS-CoV-2 and viral sepsis: observations and hypotheses.** Lancet. 2020 May 9;395(10235):1517-1520. PubMed: <https://pubmed.gov/32311318>. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)30920-X](https://doi.org/10.1016/S0140-6736(20)30920-X)

Brief but nice review and several hypotheses about SARS-CoV-2 pathogenesis. What happens during the second week - when resident macrophages initiating lung inflammatory responses are unable to contain the virus after SARS-CoV-2 infection and when both innate and adaptive immune responses are inefficient to curb the viral replication so that the patient would recover quickly?

Shen B, Yi X, Sun Y, et al. **Proteomic and Metabolomic Characterization of COVID-19 Patient Sera**. Cell May 27, 2020. Full-text:

<https://www.sciencedirect.com/science/article/pii/S0092867420306279>

Molecular insights into the pathogenesis of SARS-CoV-2 infection. The authors applied proteomic and metabolomic technologies to analyze the proteome and metabolome of sera from COVID-19 patients and several control groups. Pathway analyses and network enrichment analyses of the 93 differentially expressed proteins showed that 50 of these proteins belong to three major pathways, namely activation of the complement system, macrophage function and platelet degranulation. It was found that 80 significantly changed metabolites were also involved in the three biological processes revealed in the proteomic analysis.

Tay MZ, Poh CM, Rénia L et al. **The trinity of COVID-19: immunity, inflammation and intervention**. Nat Rev Immunol (2020). Full-text: <https://www.nature.com/articles/s41577-020-0311-8>

Brilliant overview of the pathophysiology of SARS-CoV-2 infection. How SARS-CoV-2 interacts with the immune system, how dysfunctional immune responses contribute to disease progression and how they could be treated.

Vabret N, Britton GJ, Gruber C, et al. **Immunology of COVID-19: current state of the science**. Immunity 2020, May 05. Full-text: [https://www.cell.com/immunity/fulltext/S1074-7613\(20\)30183-7](https://www.cell.com/immunity/fulltext/S1074-7613(20)30183-7)

Fantastic review on the current knowledge of innate and adaptive immune responses elicited by SARS-CoV-2 infection and the immunological pathways that likely contribute to disease severity and death.

Other key papers

Monto AS, DeJonge P, Callear AP, et al. **Coronavirus occurrence and transmission over 8 years in the HIVE cohort of households in Michigan**. J Infect Dis. 2020 Apr 4. PubMed: <https://pubmed.gov/32246136>. Full-text: <https://doi.org/10.1093/infdis/jiaa161>

It's not clear whether SARS-CoV-2 behaves like other human coronaviruses (hCoVs). A longitudinal surveillance cohort study of children and their households from Michigan found that hCoV infections were sharply seasonal, showing a peak for different hCoV types (229E, HKU1, NL63, OC43) in February. Over 8 years, almost no hCoV infections occurred after March.

Thao TTN, Labrousseau F, Ebert N, et al. **Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform**. Nature. 2020 May 4. PubMed: <https://pubmed.gov/32365353>. Full-text: <https://doi.org/10.1038/s41586-020-2294-9>

An important technical advance, enabling the rapid generation and functional characterization of evolving RNA virus variants. The authors show

the functionality of a yeast-based synthetic genomics platform to genetically reconstruct diverse RNA viruses (which are cumbersome to clone and manipulate due to size and instability). They were able to engineer and resurrect chemically-synthesized clones of SARS-CoV-2 only a week after receipt of the synthetic DNA fragments.

Gordon DE, Hiatt J, Bouhaddou M, et al. (Total: 200 authors) **Comparative host-coronavirus protein interaction networks reveal pan-viral disease mechanisms**. Science 2020, published 15 October. Full-text: <https://doi.org/10.1126/science.abe9403>

A group of 200 researchers uncovers molecular processes used by coronaviruses MERS, SARS-CoV1 and SARS-CoV2 to manipulate host cells.

5. Vaccines

Thomas Kamradt

Bernd Sebastian Kamps

Published 1 November 2020

Addendum 2 December

UK has approved the Pfizer/BioNTech mRNA COVID vaccine. Priority groups to receive the vaccine include care home care facility residents, health and care staff, the elderly and the extremely clinically vulnerable. The vaccine will be given in two doses three weeks apart. Vaccinees will be protected from SARS-CoV-2 infection from about 7 days after the second injection.

We will keep in mind that

- This is the first time that a vaccine is approved without any details published from clinical trials;
- We don't know if it works differently in different age groups;
- We don't know how long the effects of vaccination will last;
- We don't know if the vaccine (while protecting from COVID-19) is going to stop the transmission of SARS-CoV-2. In other words, we don't know if the vaccine stops people from becoming infected and infecting other people.

The major drawback of the Pfizer/BioNTech vaccine is its temperature sensitivity – it must be stored in ultra-low freezers at around minus 70-80 degrees. It also seems to be the costliest of the first 3 (Moderna, AstraZeneca).

Addendum 23 November

On November 23, Oxford University and AstraZeneca announced that their vaccine candidate [AZD1222 was highly effective in preventing COVID-19](#). No hospitalizations or severe cases of the disease were reported in participants receiving the vaccine. One dosing regimen (n=2741) showed vaccine efficacy of 90% when AZD1222 was given as a half dose, followed by a full dose at least one month apart, and another dosing regimen (n=8895) showed 62% efficacy when given as two full doses at least one month apart. The combined analysis from both dosing regimens (n=11,636) resulted in an average efficacy of 70%. AstraZeneca will soon request an authorization for early approval. In addition, the company will seek an Emergency Use Listing from the World Health Organization for an accelerated pathway to vaccine availability in low-income

countries. AZD1222 is a chimpanzee adenovirus vaccine vector which has been genetically changed so that it is impossible for it to grow in humans. It contains the full-length, unmodified spike glycoprotein of SARS-CoV-2.

AZD1222 will be less expensive and easier to store than the mRNA vaccines by BioNTech/Pfizer and Moderna (see below). It can be stored and transported at a temperature between 2 and 8 degrees Celsius and kept for six months.

Addendum 22 November

On 20 November, [BioNTech](#) and [Pfizer announced](#) that they had submitted a request to the US Food and Drug Administration for an Emergency Use Authorization of their COVID-19 vaccine candidate BNT162b2. Two days before, the two companies [announced](#) that the primary efficacy analysis showed BNT162b2 to be 95% effective against COVID-19 beginning 28 days after the first dose. Of 170 confirmed COVID-19 cases, [162 occurred in the placebo group and 8 in the vaccine group](#). Efficacy was consistent across age, gender, race and ethnicity. In particular, the observed efficacy in adults over 65 years of age was above 94%. If approved, the vaccine could be available by the end of December 2020. Find a press article at <https://www.nytimes.com/2020/11/21/us/politics/coronavirus-vaccine.html>.

On 16 November, [Moderna](#) announced that its vaccine candidate had met the primary efficacy endpoint in the first interim analysis of a Phase III study. An independent data-safety committee found that 95 trial participants had developed COVID-19 – 90 were in the placebo arm and 5 in the vaccine arm of the trial (vaccine efficacy: 94.5%).

Both the BioNTech/Pfizer and the Moderna vaccine candidates are based on messenger RNA (mRNA) technology. mRNA is comparable to a software code which instructs human cells (the ‘operating system’) to produce a SARS-CoV-2 protein. Once introduced into a cell, the mRNA molecule will be read by a ribosome and translated into the SARS-CoV-2 spike protein (see figure below). The spike protein will migrate to the cell surface where it will be recognized by the immune system as *other* and trigger an immune response.

How long (years?) might SARS-CoV-2 immunity last, was recently explored by Dan JM, Mateus J, Kato Y, et al. **Immunological memory to SARS-CoV-2 assessed for greater than six months after infection**, bioRxiv 2020, posted 16 November. Full-text: <https://doi.org/10.1101/2020.11.15.383323>. See also the press article by Mandavilli A. **Immunity to the Coronavirus May Last Years, New Data Hint**. The New York Times 2020, published 17 November. Full-text: <https://www.nytimes.com/2020/11/17/health/coronavirus-immunity.html>.

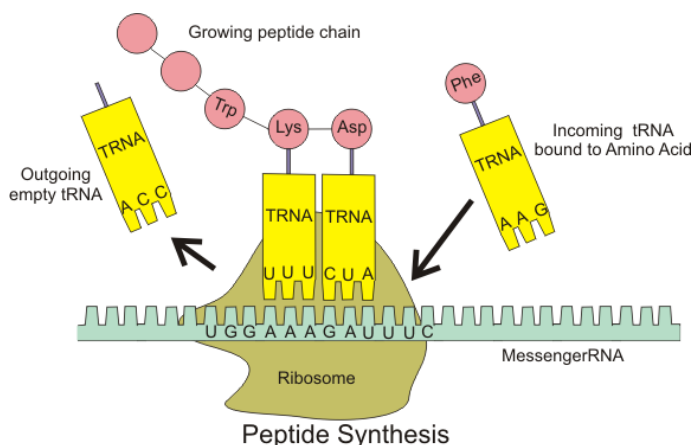


Figure 00: Ribosomes assemble protein molecules whose sequence is controlled by the sequence of messenger RNA molecules. The growing peptide chain (top left) will form the SARS-CoV-2 spike protein. tRNA: transfer RNA.

Addendum 15 November

On 9 November, [BioNTech](#) and [Pfizer](#) announced that their vaccine candidate BNT162b1 (page 222) had been found to be more than 90% effective in preventing COVID-19 in participants. Efficacy data from two other vaccine trials ([AstraZeneca](#) and [Moderna](#)) are expected this month, too. It now seems reasonable to assume that the first coronavirus vaccines could be rolled out less than a year after the discovery of SARS-CoV-2.

The BioNTech/Pfizer analysis evaluated 94 confirmed cases of COVID-19 in the participants of their Phase III trial. Two days later, the European Union [ordered 200 million doses](#) on behalf of all EU Member States, plus an option of a further 100 million doses. This could be the biggest contract ever approved after the [announcement of Phase III interim results](#).

The BioNTech/Pfizer vaccine must be stored at -70°C (-94°F) and will be sold at an amount that exceeds the manufacturing cost (\$39 for a two-dose treatment). In the future, cheaper and more convenient vaccines (storable at higher temperatures) than the BioNTech/Pfizer vaccine are needed. [AstraZeneca](#) could take the first step in the right direction if their candidate vaccine is proven to be safe and effective. The company would sell it to the British government at no profit.

* * *

Advanced SARS-CoV-2 Candidates

The development of SARS-CoV-2 vaccines will one day be recorded as one of the greatest research efforts in science. Never before have so many vaccines moved so quickly into trials for one disease (Dagotto 2020). More people will be able to get vaccinated more quickly than ever before.

An ideal pandemic vaccine would be acceptably safe for everyone, effective in inducing a durable protective immune response, rapidly scalable, stable at room temperature, single dose and cost effective (Bingham 2020). The current situation:

1. On 1 November 2020, 10 SARS-CoV-2 vaccines had reached Phase III development (Table 1 and page 207). The first preliminary trial results are expected soon.
2. So far, no vaccine has been approved after thorough clinical testing. (The “approvals” in Russia and China do not meet state-of-the-art approval criteria after thorough safety and efficacy testing.)
3. If a vaccine is shown to be both effective and safe, it will first be offered to risk groups and essential professionals (medical staff, elderly people, police, fire fighters, etc.)
4. Massive nationwide vaccine campaigns will not be available until well into 2021.
5. Massive global vaccine campaigns are unlikely to have a more than marginal impact on the SARS-CoV-2 pandemic before 2022, if ever.

Data from Phase II trials show that adverse effects, although generally not severe, are nonetheless frequent (rule of thumb: 50%) – pain at injection site, hyperthermia, headache, asthenia, muscle and joint pain (Folegatti 2020, Zhu 2020, Jackson 2020, Mulligan 2020, Logunov 2020). The “Big Three” vaccines in Phase III for which results are expected within the next months are:

- BNT162b2 (BioNTech/Pfizer/Fosun)
- ChAdOx1 (University of Oxford/AstraZeneca)
- mRNA-1273 (Moderna/NIH)

The Future of SARS-CoV-2 vaccines

Questions

The questions which are currently being addressed in Phase III vaccine trials have been summarized by Naor Bar-Zeev and William Moss ([Bar-Zeev 2020](#)):

- Will a single dose be sufficient in older adults, or is a booster dose required?
- Does longevity of response or rates of waning differ with a two-dose regimen, and does longevity of clinical protection require cell-mediated responses?
- Are there host-specific differences in immunogenicity by age, sex, or ethnicity?
- Do T cell responses correlate with protection irrespective of antibody titers?
- Are there specific adverse events in pregnant women?

After the beginning of mass vaccinations, more questions will arise:

- How will risk groups fare (e.g. elderly people with hypertension, diabetes, obesity, etc.)?
- Are re-vaccinations needed at regular intervals?
- Will SARS-CoV-2 mutate so that the vaccines will have to be adapted like the annual flu vaccines?

Vaccine Approval

As of 1 November 2020, no vaccine had been approved after thorough safety and efficacy testing.

Efficacy

WHO recommends that successful vaccines should show an estimated risk reduction of at least one-half ([WHO 20200409](#)). Well aware of the fact that rushing an ineffective or unsafe vaccine to the market could do substantial damage to people and their reputation, on 8 September 2020, nine pharmaceutical companies (AstraZeneca, BioNTech, Pfizer, Moderna, GlaxoSmithKline, Johnson & Johnson, Merck, Novavax and Sanofi) issued a joint pledge that they would “stand with science” and not put forward a vaccine until it had been thoroughly vetted for safety and efficacy ([Thomas 2020](#)).

Table 1. Vaccines in Phase III trials*

Developer	Candidate vaccine	Vaccine platform	Reference	News release
AstraZeneca / Oxford University (NCT04324606)	ChAdOx1	Non-replicating vector	Folegatti 2020	28 June '20
Pfizer / BioNTech / Fosun (NCT04368728)	BNT162b1	RNA	Mulligan 2020	27 July '20
Moderna / NIAID (NCT04283461)	mRNA-1273	RNA	Jackson 2020	27 July '20
Sinovac Biotech (NCT04352608)	CoronaVac	Inactivated	Gao 2020	6 July '20
CanSino Biologics / Beijing Institute of Biotechnology (NCT04341389)	CTII-nCoV	Replication-incompetent vector	Zhu 2020	
Wuhan Institute of Biological Products / Sinopharm (ChiCTR2000031809)		Inactivated	Xia S 2020	
Beijing Institute of Biological Products / Sinopharm		Inactivated		
Novavax (NCT04533399)	NVX-CoV2373	Replication-incompetent vector	Keech 2020	2 Sep '20
Janssen (Johnson & Johnson; NCT04505722)	Ad26.COVS.S		Mercado 2020	NYTimes 17 July '20
Gamaleya Research Institute (NCT04530396)	Sputnik V	Replication-incompetent vector	Logunov 2020, Bucci 2020	NYTimes 11 August '20

* In Phase III trials, a vaccine is given to tens of thousands of people (50% will receive the true vaccine, 50% will receive a placebo injection) in order to show efficacy and reveal evidence of relatively rare side effects that might have been missed in earlier studies. The FDA expects that an acceptable COVID-19 vaccine would prevent disease or decrease its severity in at least 50% of people who are vaccinated ([FDA 20200630](#)).

Humane challenge studies

Human challenge studies (HCS) could assess the effectiveness of experimental vaccines more rapidly and thereby accelerate vaccine development. The prospect of deliberately infecting young adults — even those at low risk of severe disease — with SARS-CoV-2, a deadly pathogen that has few proven treatments, is uncharted medical and bioethical territory (Callaway 2020, Deming 2020). Typically, undertaking human challenge studies in vaccine development requires that the disease for which a challenge would be introduced either has an available rescue therapy to treat those who become infected or the disease is known to be self-limiting (Kahn 2020).

In the UK, the first COVID-19 human challenge studies could begin in January 2021. The first phase aims to discover the smallest amount of virus it takes to cause the infection in up to 90 healthy young people, aged between 18 and 30 years, who are at the lowest risk of harm from COVID-19 (Kirky 2020, Cookson 2020).

WHO has published criteria for the ethical acceptability of COVID-19 human challenge studies (WHO 20200506). An ethical study design would involve healthy participants in inpatient settings with immediate access to high-quality health care and strict infection control measures (Jamrozik 2020). Some authors argue that human challenge studies face unacceptable ethics challenges, and, further, undertaking them would do a disservice to the public by undermining already strained confidence in the vaccine development process (Kahn 2020). If the studies proceed, it will be interesting to understand the relationship between efficacy data from human challenge studies in young individuals and protection of the elderly — the population which is at highest risk from SARS-CoV-2 infection (Hodgson 2020).

Setbacks

Vaccine development is fraught with obstacles. As demonstrated by the ChAdOx1 experience (Oxford/AstraZeneca), serious adverse events can at any time grind a trial to a halt (Phillips 2020). Should a transverse myelitis (Shah 2020) be recognized as triggered by the vaccine, the trial would be stopped immediately. Vaccine-related adverse events, either debilitating or fatal, might even be recognized years after approval and lead to the withdrawal of the vaccine. Both the public and vaccine developers should be prepared for unanticipated turns in the COVID Vaccine Saga. There is a piece of good news, though: the D614G mutation of the SARS-CoV-2 spike protein does not seem to affect adversely the efficacy of vaccines (McAuley 2020).

Vaccine distribution

Access to a safe vaccine might be unequal, both within countries and between them. Within countries, health authorities will prepare strategic prioritization plans (Lipsitch 2020). Vaccines will be offered first to healthcare workers; then to people at high risk of severe COVID-19 and maybe those living in epidemiological hotspots; and, finally, to the rest of the population – if they want to get vaccinated (Schwartz 2020, Bingham 2020). Between countries, there is no doubt that those that produce vaccines will get the vaccine before countries that don't. On 24 August 2020, wealthy countries had pre-ordered around two billion vaccine doses without knowing which one may prove effective (see an overview of the August situation in Callaway 2020). However, it is not acceptable that low-risk people in wealthy countries get the vaccine while health care workers in low- and middle-income countries do not. To avoid such a scenario, GAVI, the Vaccine Alliance (a Geneva-based funder of vaccines for low-income countries), the Coalition for Epidemic Preparedness Innovation (CEPI²) and the World Health Organization have set up the COVID-19 Vaccines Global Access (COVAX) Facility (Kupferschmidt 2020, Jeyanathan 2020). COVAX aims to accelerate the development and manufacture of COVID-19 vaccines, and to guarantee fair and equitable access for every country in the world by securing 2 billion vaccine doses. One billion have already been reserved for 92 low- and middle-income countries and economies (LMICS), which make up half the world's population.

Impact of vaccines on the pandemic

A vaccine against SARS-CoV-2 might act against infection, disease, or transmission and a vaccine capable of reducing any of these elements could contribute to disease control (Hodgson 2020). It is too early to predict if SARS-CoV-2 vaccines will have a measurable impact on the course of the SARS-CoV-2 pandemic over the coming years.

² The Coalition for Epidemic Preparedness Innovation (CEPI), an international nongovernmental organization funded by the Wellcome Trust, the Bill and Melinda Gates Foundation, the European Commission, and eight countries (Australia, Belgium, Canada, Ethiopia, Germany, Japan, Norway, and the United Kingdom), is supporting development of vaccines against five epidemic pathogens on the World Health Organization (WHO) priority list (Lurie 2020).

Vaccines in Phase III

ChAdOx1

ChAdOx1, developed by the University of Oxford, AstraZeneca and the Serum Institute of India, uses replication-deficient simian adenovirus vector ChAdOx1 which contains the full-length, unmodified structural surface glycoprotein (spike protein) of SARS-CoV-2. Results from a Phase I/II randomized trial showed that in ChAdOx1 vaccinees, T cell responses peaked on day 14, anti-spike IgG responses rose by day 28, and neutralizing antibody responses against SARS-CoV-2 were detected in > 90%. Adverse events such as fatigue, headache, and local tenderness commonly occurred, but there were no serious adverse events (Folegatti 2020).

BNT162b1

BNT162b1, developed by BioNTech, Pfizer and Fosun, is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine³ that encodes trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain. Early studies indicated that well-tolerated dose levels of BNT162b1 efficiently elicited high titer, broad serum neutralizing responses, Th1 phenotype CD4⁺ T helper cell responses, and strong interferon γ and interleukin-2 producing CD8⁺ cytotoxic T-cell responses (Sahin 2020, Mulligan 2020). On 27 July, the companies announced a Phase II/III trial with 30,000 volunteers in the US, Germany, Argentina, and Brazil, among others. If the clinical studies are successful, BioNTech and Pfizer want to apply for approval of the vaccine as early as this year. If approved, BioNTech, Pfizer and Fosun could manufacture up to 100 million vaccine doses by the end of 2020 and over 1.3 billion by the end of 2021.

³ mRNA vaccines: Two mRNA vaccine formulations against COVID-19 have now been tested in tens of thousands of volunteers: one developed by a collaboration between Pfizer and BioNTech, and the other by Moderna and the National Institute of Allergy and Infectious Diseases (NIAID) in the US (Nat Biomed Eng 2020). mRNA vaccines like BNT162b2 have the potential to be truly transformative but have never been tested in large-scale human trials; see Abbasi 2020 for a tour of mRNA vaccines today and beyond COVID-19. BioNTech, Moderna, CureVac and GSK own nearly half of the mRNA vaccine patent applications (Martin 2020).

mRNA-1273

mRNA-1273, developed by Moderna, is a lipid nanoparticle-encapsulated, nucleoside-modified messenger RNA (mRNA)-based vaccine that encodes the SARS-CoV-2 spike (S) glycoprotein stabilized in its prefusion conformation. mRNA-1273 induced potent neutralizing antibody responses to both wild type (D614) and D614G mutant² SARS-CoV-2 as well as CD8⁺ T cell responses, and protects against SARS-CoV-2 infection in mice (Corbett 2020) and non-human primates (Corbett 2020b). In early clinical trials, it induced anti-SARS-CoV-2 immune responses in all participants, and no trial-limiting safety concerns were identified (Jackson 2020). The Phase III trial, launched on 27 July 2020, will enroll 30,000 healthy people in the US.

CoronaVac (Sinovac)

CoronaVac[®] is an inactivated virus vaccine developed by Sinovac Biotech, Ltd. In macaques, the vaccine provided partial or complete protection against a SARS-CoV-2 challenge (Gao 2020). In September 2020, the company reported data from healthy adults aged 60 years and above in Phase I/II clinical trials where the seroconversion rate for elderly participants would have been comparable to that in a group of 18 to 59 years healthy people. The data have not yet been published in a peer-reviewed journal. Phase III trials enrolled 24,000 people in Brazil, Indonesia and Turkey. Enrolment of children younger than 18 started in September 2020. The company is planning to produce 300 million vaccine doses in 2021.

CTII-nCoV

CTII-nCoV, developed by CanSino Biologics in partnership with the Institute of Biology at the Chinese Academy of Military Medical Sciences, is based on an adenovirus called Ad5. Results from Phase II trials demonstrated that the vaccine produced significant neutralizing antibody responses to live SARS-CoV-2 (Zhu 2020). In a Phase II trial, a single injection of the Ad5-vectored COVID-19 vaccine at 1×10^{11} viral particles and 5×10^{10} viral particles induced comparable specific immune responses to the spike glycoprotein at day 28. Positive specific T cell responses were found in 90% and 88% of participants receiving the vaccine at 1×10^{11} and 5×10^{10} viral particles, respectively. 95% of participants in the 1×10^{11} viral particles dose group and 91% of the recipients in the 5×10^{10} viral particles dose group showed either cellular or humoral immune responses at day 28 post-vaccination (Zhu 2020). The authors found that compared with the younger population, older people had a significantly lower immune response, but higher tolerability, to the Ad5-vector COVID-19 vaccine. Pre-existing immunity to the Ad5 vector and increasing age could partially hamper the specific immune responses to vaccination,

particularly for the humoral immune responses. Adverse events such as fever, fatigue, headache, or local site pain were comparable to the ChAdOx1 study above.

On 25 June, the Chinese military [approved](#) the vaccine for a year as a “special-ly needed drug.” CanSino would not say whether vaccination was to be mandatory or optional for soldiers.

Wuhan Institute vaccine

An inactivated virus vaccine developed by the Wuhan Institute of Biological Products, put into clinical trials by the state-owned Chinese company Sinopharm, showed that the vaccine produced antibodies in volunteers ([Xia S 2020](#)). Some volunteers experienced fevers and other side effects. Phase III trials are under way in China, Peru, Morocco and the United Arab Emirates.

Beijing Institute vaccine

Another inactivated virus vaccine developed by the Beijing Institute of Biological Products (again put into clinical trials by Sinopharm), is currently being tested in Phase III trials in China and in the United Arab Emirates.

NVX-CoV2373

NVX-CoV2373, developed by Novavax, is a recombinant nanoparticle vaccine (rSARS-CoV-2) composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant ([Keech 2020](#)). In a Phase I/II trial, the vaccine induced levels of neutralizing antibodies that closely correlated with anti-spike IgG. After the second vaccination neutralizing antibody responses exceeded values seen in symptomatic COVID-19 outpatients and were of the magnitude seen in convalescent serum from hospitalized patients with COVID-19.

Ad26.COV2.S

Ad26.COV2.S, developed by Janssen, is a recombinant replication-incompetent adenovirus type 26 (Ad26) vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen. Its potency in eliciting protective immunity against SARS-CoV-2 infection was successfully demonstrated in a non-human primate challenge model ([Mercado 2020](#)). Ad26.COV2.S induced robust neutralizing antibody responses and provided complete protection against a SARS-CoV-2 challenge in five out of six rhesus macaques and near-complete protection in one out of six macaques ([Mercado 2020](#)). The vaccine platform for the development of this optimized S protein-

based vaccine has been recently described ([Bos 2020](#)). A Phase III study plans to enrol up to 60,000 participants.

Sputnik V

Sputnik V (formerly Gam-COVID-Vac Lyo), developed by the Gamaleya Research Institute, is a combination of two adenoviruses, Ad5 and Ad26, each carrying an S antigen of the new coronavirus. Phase III trials, initially planned for just 2,000 volunteers, were expanded to 40,000.

Immunization Fundamentals

The SARS-CoV-2 pandemic and the unprecedented research effort to develop multiple vaccines on different platforms is a good occasion to recall some immunization fundamentals. Recovery from infections often induces long-term and sometimes life-long immunity against the causative pathogen. After the resolution of the infection, immunological memory protects against re-infection and is mediated by specific antibodies and T-cells.

In contrast, immunizations confer immunity without exposure to virulent pathogens. Immunization can be passive or active. In passive immunisation protective antibodies are transferred from a donor into a recipient whereas active immunization induces a protective immune response in the recipient.

Passive immunization against SARS-CoV-2

Passive immunization against SARS-CoV-2 can be achieved with convalescent plasma or with neutralizing monoclonal antibodies.

Convalescent plasma

Treatment with human convalescent plasma (CP) is based on the assumption that protective antibodies against the causative pathogen are present in the blood of people who have overcome an infectious disease. For example, CP has been used to treat some infectious diseases such as Argentine hemorrhagic fever ([Casadevall 2004](#)). CP was also used to treat SARS patients in the 2002/2003 epidemic but not in controlled clinical studies; a later meta-analysis concluded that the treatment was probably safe and perhaps helpful ([Mair-Jenkins 2015](#)).

CP could become an option for prevention and treatment of COVID-19 disease when there are sufficient numbers of people who have recovered and can donate immunoglobulin-containing serum ([Casadevall 2020](#)). Antibodies that are found in CP are very stable. Pathogen inactivation (using psoralen and UV light) did not impair the stability and neutralizing capacity of SARS-CoV-2-

specific antibodies that was also preserved at 100% when the plasma was shock frozen at -30°C after pathogen-inactivation or stored as liquid plasma for up to 9 days (Tonn 2020). However, in a recently published open label randomized controlled trial (the largest to date with results) 464 patients were assigned either to two doses of 200 mL CP or best standard of care only. The result was sobering: progression to severe disease or all-cause mortality at 28 days after enrolment occurred in 44 (19%) participants in the CP arm and 41 (18%) in the control arm (Agarwal 2020).

The major caveat of CP is quantity and quality of antibody titers. In plasma from 149 patients collected on average 39 days after the onset of symptoms, neutralizing titers were extremely variable. Most plasmas did not contain high levels of neutralizing activity (Robbiani 2020). There seems to be a correlation between serum neutralizing capacity and disease severity, suggesting that the collection of CP should be restricted to those with more severe symptoms (Chen 2020). Another, unintended, consequence of receiving CP may be that recipients will not develop their own immunity, putting them at risk for re-infection.

In addition, in light of the possibility of antibody-dependent disease enhancement (ADE), safety is still a hypothetical consideration in the ongoing CP trials. One study on macaques found that passive transfer of anti-SARS-CoV-S immunoglobulin from immunized monkeys into naïve recipients resulted in acute lung injury after infection. The proposed mechanism was a diversion of macrophage activation from wound healing to pro-inflammatory (Liu 2019). Enhanced lung-pathology upon antibody-transfer was also observed in a rabbit model of MERS (Houser 2017). Convalescent plasma has been given to MERS patients and one case-report raises the possibility of acute lung injury following convalescent plasma transfusion (Chun 2016).

The future development of anti-SARS-CoV-2 convalescent plasma should take into account 1) the potential harms of the non-immune components of convalescent plasma (especially prothrombotic risks); 2) that only donor plasma with detectable titers of neutralizing antibodies be given to trial participants; 3) ensure double blind designs with placebo controls as the gold standard for future trials; 4) preclude non-immune plasma as a control intervention, because of potential harms and availability of lower risk alternatives such as normal saline (Pathak 2020).

Find more information on CP in the *Treatment* chapter, page 347.

Monoclonal antibodies

Competition is heating up to produce targeted monoclonal antibodies which could both prevent and treat COVID-19 (Cohen 2020). The development of highly successful monoclonal antibody-based therapies for cancer and immune disorders has created a wealth of expertise and manufacturing capabilities (Biopharma 2020) and neutralising monoclonal antibodies are now a plausible therapeutic option against infectious diseases (Marston 2018). Monoclonal antibodies against rabies virus and against the respiratory syncytial virus (RSV) are approved for the treatment of patients and other monoclonal antibodies are in advanced stages of clinical trials (Walker 2018). Both protective and pathogenic effects were observed (Wang Q 2016, Chen X 2020).

SARS-CoV-2 neutralizing human monoclonal antibodies were intensely studied in 2020 (Robbiani 2020, Wec 2020, Ju B 2020). It was shown that REGN-CoV-2, a cocktail of two antibodies, might preclude the appearance of escape mutants (Baum 2020) and decrease virus-induced pathological sequelae in rhesus macaques (Baum 2020b). In hamsters, the cocktail limited weight loss and evidence of pneumonia in the lungs. The first (not yet peer reviewed!) published clinical results of REGN-CoV-2 describe the results in non-hospitalized COVID-19 patients with symptom onset ≤ 7 days from randomization and not on any putative COVID-19 therapy. After single doses of REGN-CoV-2 at 2.4 g IV (lower dose), 8 g IV (higher dose) or placebo, the company found a reduction of “viral load” in nasopharyngeal (NP) swabs of -1.92 and -1.64 log₁₀ copies/mL, compared to -1.41 with placebo (Regeneron 2020). These results are not particularly impressive.

The ‘COVID-19 antibody sphere’ features companies like Amgen, AstraZeneca, Vir, Regeneron, Lilly and Adagio (Biopharma 2020). However, the future role of monoclonal antibodies as a bridging solution before the general availability of vaccines and efficient antiviral drugs is unclear. These drugs are complex and expensive to produce, leaving people from poor countries locked out (Ledford 2020, Ledford 2020b) and fears have been voiced that they could split the world into the haves and have-nots, like many other drugs before (Cohen 2020). Fortunately, these fears may not materialize. As soon as the first truly effective antiviral drugs become available – as for HSV in 1981, HIV in 1996 and HCV in 2013 – there will be no need for monoclonal antibodies anymore.

Find more details on monoclonal antibodies in the *Treatment* chapter, page 343.

Active immunization against SARS-CoV-2

At the time of this writing (October 2020), there are more than 170 COVID-19 vaccine candidates in different stages of preclinical development. Ten candidate vaccines are in Phase III clinical trials ([Thanh Le 2020](#)). If one considers that the development of a vaccine usually takes well over 10 years to complete ([Heaton 2020](#)), it becomes clear how quickly progress is being made ([Slaoui 2020](#)).

This rapid development is based on a massive global effort, including the parallelization of development and production steps that have traditionally been carried out sequentially ([Lurie 2020](#)), the knowledge generated in attempts to develop vaccines against SARS-CoV-1 and MERS-CoV, and innovative techniques ([Hekele 2013](#)) that were not available until recently. The speed of SARS-CoV-2 vaccine development is breathtaking. On 11 January 2020 Chinese researches published the sequence of the SARS-CoV-2 genome on the internet. Approximately 2 months later, on 16 March, an mRNA-based vaccine entered a Phase I clinical trial ([Arnold 2020](#)).

Earlier work had identified the S protein of SARS-CoV and MERS-CoV as a suitable vaccine target. The S protein binds to its cellular receptor, ACE2, to infect human cells. With the sequencing of the genome of SARS-CoV-2, the high homology between the S proteins of the 3 viruses was known and a little later the interaction of SARS-CoV-2 with ACE was confirmed ([Hoffmann 2020](#)). A relevant target structure for immune responses was identified in record time.

However, there are still some hurdles to overcome in vaccine development. This includes the fact that the correlates of protective immunity against SARS-CoV-2 are currently incompletely understood, that the available data indicate that immunity against SARS-CoV-2 may not be very long-lasting and that preclinical studies on vaccine candidates against SARS-CoV and MERS-CoV have given indications of possible side effects (see below).

SARS-CoV-2 vaccine platforms

The platforms used for SARS-CoV-2 vaccine developments have recently been summarized in an excellent review by Florian Krammer ([Krammer 2020](#)). Current SARS-CoV-2 vaccine candidates include (the letters in the brackets refer to [Figure 3](#) of the Krammer review):

- inactivated virus vaccines (c)
- live attenuated vaccines (d)

- recombinant protein vaccines based on the spike protein (e), the RBD (f) or on virus-like particles (g)
- replication-incompetent vector vaccines (h)
- replication-competent vector vaccines (i)
- inactivated virus vector vaccines that display the spike protein on their surface (j)
- DNA vaccines (k)
- RNA vaccines (l)

The most traditional way to produce vaccines is the use of **whole viruses**, which are either *attenuated* or *inactivated*. Currently licensed examples include the vaccines against measles and yellow fever (attenuated virus) and influenza and polio (inactivated viruses). Two inactivated vaccines protect rhesus monkeys from SARS-CoV-2. The vaccines were well tolerated preclinically; in particular, no type 2 immunopathology was found in the lungs (see below: pathological immune responses) (Gao Q 2020, Wang H 2020). Various vaccines that use inactivated SARS-CoV-2 as an immunogen are currently available in different phases of clinical trials, three of which are already in Phase III studies (WHO Landscape 2020).

Another approach is to use **recombinant viral proteins** as vaccine; licensed examples include the vaccines against hepatitis B and human papilloma virus. Efforts are ongoing to develop recombinant SARS-CoV-2 S protein as an immunogen. Nine vaccines that use recombinant SARS-CoV-2 S protein as an immunogen are in the early phases of clinical trials (Phase I or I/II) (WHO Landscape 2020).

A more recent approach is to use **recombinant viral vectors** in which a relevant antigen of the pathogenic virus is expressed.

Currently, the Ebola vaccine is the only approved vaccine based on this principle (Henao-Restrepo 2017). A recombinant vaccine protected rhesus monkeys from SARS-CoV-2. The vaccine was well tolerated; in particular, no type 2 immunopathology was found in the lungs (see below: pathological immune responses) (van Doremalen 2020). Three different adenovirus-based recombinant vaccines against SARS-CoV-2 are currently in clinical Phase III studies (WHO Landscape 2020). A potential problem with these vaccines could be pre-existing immune responses of the vaccinees against adenoviruses (Zhu FC 2020).

Four **DNA vaccines** against SARS-CoV-2 are currently in the early phases of clinical trials (Phase I or I/II) (WHO Landscape 2020). There are currently no

approved DNA vaccines, which could make the approval process more complicated compared to other vaccines.

An mRNA vaccine intended to induce immune responses against SARS-CoV-2 was already tested in a clinical Phase I study in March 2020 (Jackson 2020). Two mRNA vaccines are currently in Phase III clinical trials, another is in a Phase II trial, and others are in earlier phases of clinical trials (WHO Landscape 2020). The approval process for RNA vaccines could be more complicated than for conventional vaccines because currently there are no approved mRNA vaccines for any indication.

Issues to address during vaccine development

Vaccines against coronaviruses can induce pathological immune responses.

Rarely, vaccines can enhance disease rather than protect from disease (Kim 1969, Openshaw 2001). Some vaccine candidates against SARS-CoV-1 or MERS-CoV have caused disease-intensifying immunopathological effects in some pre-clinical models. The safety of a vaccine against SARS-CoV-2 is of course of essential importance (Lambert 2020).

Immunization with recombinant SARS-CoV spike (S) -coding modified vaccinia virus Ankara (rMVA) causes hepatitis in ferrets.

Ferrets are susceptible to SARS-CoV and SARS-CoV-2 infections (Kim YI 2020). Weingartl et al. immunized ferrets with a recombinant modified vaccinia virus Ankara (rMVA), which encoded the SARS-CoV S protein (Weingartl 2004). After infection with the virus, high titers of neutralizing antibodies were detectable in the immunized animals. Nevertheless, the immunized infected ferrets developed severe hepatitis while the non-immunized did not (Weingartl 2004).

Type 2 immunopathology in the lungs of immunized mice

Bolles et al. (Bolles 2011) immunized mice with inactivated SARS-CoV with or without adjuvant. The vaccine protected young and old animals from morbidity and mortality after infection with high doses of virus. If the mice were infected with a heterologous virus strain, the immunized animals developed more pronounced inflammatory infiltrates and pulmonary eosinophilia than the non-immunized (Bolles 2011). These results were later confirmed by another working group (Tseng CT 2012). Eosinophilic lung infiltrates were also observed in mice after immunization with a recombinant baculovirus (S protein) or coronavirus-like particles (VLPs) that expressed SARS-CoV S protein.

It is important to note that these are histopathological findings; the immunized mice still had reduced virus titers after infection (Tseng CT 2012, Loku-gamage 2008). Nevertheless, the findings are worrying. They are similar to the histopathological changes seen in the 1960s in children who became ill after immunization with a vaccine against RSV (Castilow 2007). Pathological changes in the lungs and even pneumonia after infection with SARS-CoV were also observed in mice in other SARS-CoV vaccine candidates (Yasui 2008).

Similar findings have been reported for vaccine candidates for MERS-CoV. An inactivated MERS-CoV vaccine induced neutralizing antibodies in mice. Nevertheless, after infection, the immunized mice developed an increased type 2 pathology in the lungs with increased eosinophilic infiltrates and increased concentrations of IL-5 and IL-13 (Agrawal 2016). Recent studies suggest that the development of type 2 immunopathology can be influenced by the choice of appropriate adjuvants, e.g. TLR ligands, for inactivated viruses, or recombinant S protein can be avoided (Iwata-Yoshikawa 2014, Honda-Okubo 2015).

Overall, these findings are a clear indication that during the preclinical development of vaccines against SARS-CoV-2, an intensive search should be made for immunopathological changes in the lungs of the immunized animals. It is encouraging that many of the pre-clinical studies published to date on SARS-CoV-2 vaccine candidates explicitly indicate that such changes have been sought and not found.

Type 2 immunopathology in the lungs of immunized primates

In a recent study Chinese macaques were vaccinated with a modified vaccinia Ankara (MVA) virus encoding full-length SARS-CoV S glycoprotein (ADS-MVA) and challenged with SARS-CoV 8 weeks later (Liu 2019). Vaccination induced high levels of antibodies and reduced virus loads. However, the vaccinated monkeys had diffuse alveolar damage (DAD) (Liu 2019). These findings are similar to those of an earlier study in which macaques were immunized with inactivated SARS-CoV. Three monkeys were protected upon challenge whereas one macaque had lung pathology consistent with antibody-dependent disease enhancement (ADE) (Wang 2016). The authors suspect that only antibodies against certain SARS-CoV S epitopes induce the immunopathology. In the previously published SARS-CoV-2 vaccination studies in monkeys, no lung pathology was observed (Gao Q 2020, Wang H 2020, van Doremalen 2020). Overall, there is no evidence of immunopathology after vaccination and infection in the preclinical studies published to date.

Questions for the Future

The diverse and massive efforts in vaccine development and the unprecedented pace of progress give rise to hope that an effective and safe vaccine will soon be available. However, some important questions remain unanswered.

Correlates of Protection

Knowledge about the immune responses against SARS-CoV-2 is growing rapidly (Vabret 2020); it seems clear that neutralizing antibodies against the S protein can mediate protection. SARS-CoV-2-specific T cells can also be present in people without detectable antibodies against SARS-CoV-2 (Braun 2020, Grifoni 2020, Sekine 2020). Preclinical studies on SARS (Li CK 2008) and MERS (Zhao J 2017) suggest that virus-specific CD4+ (Zhao J 2016) and CD8+ (Channappanavar 2014) T cells can be protective even in the absence of serologically detectable antibodies (Tang F 2011).

Longevity of the immunological memory against SARS-CoV-2

Ideally, a vaccine induces long-term immunity; unfortunately, this goal may not be realistic for SARS-CoV-2. Infections with common cold coronaviruses generate only a short-lived immunity. Experiments from the 1980s have shown that just one year after inoculation with coronavirus 229E, the majority of the test subjects could be infected again. They did have milder symptoms than non-inoculated subjects, so a certain protection was seen despite renewed infection (Callow 1990).

Experiences from the 2002-2004 SARS-CoV outbreak, too, suggest that SARS-CoV-2 immune responses will be short-lived. Six years after having suffered SARS disease, antibodies to SARS-CoV were no longer detectable in 21/23 patients (Tang F 2011). In contrast, SARS-CoV-specific T cells were still detectable, which suggests the possibility that T cell memory against corona viruses may be more long-lasting than serological memory (Tang F 2011). Similar findings have been described for the immune response after MERS disease (Zhao J 2017); however, there is currently no reliable knowledge about the longevity of T cell memory against SARS-CoV 2. There have been reports of renewed SARS-CoV-2 infections after surviving the first infection (To KK 2020).

After almost one year of research, the picture of immunological memory against SARS-CoV-2 is becoming clearer. The kinetics of the neutralizing antibody response to SARS-CoV-2 is typical of an acute viral infection where a peak response is detected 3-4 weeks post-infection, which then wanes (Seow

2020). More than 90% of infected individuals with mild-to-moderate COVID-19 experience might develop robust IgG antibody responses against the viral spike protein and titers will be relatively stable for months. Anti-spike binding titers correlate with neutralization of authentic SARS-CoV-2 (Gudbjartsson 2020, Wajnberg 2020, Alter 2020). Patients with a worse clinical classification may have higher neutralizing antibody titer (Wang X 2020).

However, asymptomatic individuals have a weaker immune response to SARS-CoV-2 infection than patients with severe COVID-19 (Long QX 2020) and humoral immunity against SARS-CoV-2 may not be long lasting in this large group that composes the majority of infected persons (Ibarrondo 2020, Weis 2020). One group showed that in individuals who develop a low neutralizing antibody response (ID_{50} 100–300), titers can return to baseline over a relatively short period, whereas those who develop a robust neutralizing antibody response maintain titers $> 1,000$ despite the initial decline (Seow 2020).

Pre-existing immune responses against SARS-CoV-2

SARS-CoV-2-specific CD4+ and CD8+ T lymphocytes can be detected in around 20 to 100% of non-exposed healthy volunteers (Braun 2020, Grifoni 2020, Mateus 2020, Bacher 2020). It has been speculated that these cross-reactive T lymphocytes could be protective against SARS-CoV-2 or influence the course of the disease. As a matter of fact, it is known that cross-reactive T cells can influence the course of viral infections both positively and negatively (Ngono 2018). Antibodies that neutralize SARS-CoV-2 have also been detected in uninfected and non-exposed healthy volunteers (Ng KW 2020).

We might not rely on protection without exposure, though. In a recently published pre-print study from Rockefeller University, the authors measured neutralizing activity against SARS-CoV-2 in pre-pandemic sera from patients with prior PCR-confirmed seasonal coronavirus infection. While neutralizing activity against seasonal coronaviruses was detected in nearly all sera, cross-reactive neutralizing activity against SARS-CoV-2 was undetectable (Posten 2020). The authors conclude that while it is possible that there are rare instances of individuals possessing antibodies from prior seasonal HCoV infection who may be able to also target SARS-CoV-2 S, their data would argue against a broad role for pre-existing protective humoral immunity against SARS-CoV-2.

Recently, a provocative concept was introduced by Alexander Scheffold and colleagues. The authors propose the immunological age as an independent risk factor to develop severe COVID-19 (Bacher 2020). Their reasoning:

1. Unexposed individuals harbor SARS-CoV-2-specific memory T cells with marginal cross-reactivity to common cold corona and other unrelated viruses.
2. These T cells display low functional avidity and broad protein target specificities and their frequencies correlate with the overall size of the CD4+ memory compartment reflecting the immunological age of an individual.
3. COVID-19 patients generate strong pro-inflammatory T cells responses, that increase with disease severity.
4. Unexpectedly, severe disease is associated with lower functional avidity and TCR clonality.
5. Low avidity pre-existing T cell memory negatively impacts on the T cell response against neoantigens such as SARS-CoV-2, which may predispose to develop inappropriate immune reactions especially in the elderly.

Find more about this topic in the 6th edition of COVID Reference.

Outlook

Vaccines are the most potent medical products of all times to prevent morbidity and mortality. Over the last two centuries, no other medical intervention has saved as many lives. Without vaccines, many of today's anti-vaccine activists ([Burki 2020](#)) would not have been born (and maybe neither you nor me) because of lack of ancestors – one or more of them would have succumbed to infectious disease before reaching mating age. Vaccines train the body's immune system to recognize and fight pathogens and on the next exposure to the pathogen, the immune system is ready to fight the invader off. The vaccination procedure is simple: introduce certain molecules from the pathogen into the body and trigger an immune response. Vaccines are 'elegant medicine' – they prevent rather than treat a disease.

At the end of this COVID Year One, virology, biologic chemistry and immunology are the celebrated fields of medicine. Virology explores the structure and functioning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and, together with biologic chemistry, prepares the terrain for future drug development. In the meantime, immunology explores the virus-human interface and describes how the human body fights back and forms a memory after the first encounter with SARS-CoV-2: it examines why most people recover from the infection while a few die and other remain disabled; and it contributes to the understanding of the biological mechanisms that lead to illness and death. Why do older people die from coronavirus disease

2019 (COVID-19) while younger people don't? Why are people with hypertension, diabetes or obesity at increased risk of severe COVID-19? Immunology also tries to elucidate the mystery of superspreader individuals, those few acutely SARS-CoV-2 infected people who are thought to be responsible for the vast majority of transmissions. Finally, immunology will spin out the most powerful antiviral weapon: vaccines.

One challenge for the developers of COVID-19 vaccine(s) is that the elderly are most susceptible to the infection and carry a particularly high risk for severe or lethal disease. Due to immunosenescence, the elderly are notoriously difficult to immunize, requiring higher doses or particular immunization schemes in order to generate a protective immune response. Studies in mice indicate that older animals are also more likely to develop immunopathology upon vaccination.

The SARS-CoV-2 pandemic is a colossal challenge for healthcare systems and societies. It is also the time of the 'Great Rehearsal'. By coordinating global resources and supra-national structures to react swiftly, science is currently creating the infrastructure to fight any other new and potentially far deadlier viral disease that emerges in the future. SARS-CoV-2 is not the last pathogen humanity will have to deal with in the 21st century and more enzootic viruses will jump from their animal reservoirs to humans. However, after this pandemic, hopefully we will be better prepared for future challenges, with new vaccine platforms that can quickly be adapted to newly emerging viral diseases. There is even a final twist to the unexpected events of 2020: the SARS-CoV-2 pandemic is opening up a new era of vaccine development. In 10 years we can expect to have a wide range of new and innovative vaccines we would not have dared to previously dream of.

Weekend Reference

If you have not read this article, read it next weekend: Krause P, Fleming TR, Longini I, Henao-Restrepo AM, Peto R; World Health Organization Solidarity Vaccines Trial Expert Group. **COVID-19 vaccine trials should seek worth-while efficacy.** Lancet. 2020 Aug 27:S0140-6736(20)31821-3. PubMed: <https://pubmed.gov/32861315>. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31821-3](https://doi.org/10.1016/S0140-6736(20)31821-3). Brilliant review of SARS-CoV-2 vaccines: vaccine platforms, results from studies on non-human primates and results from Phase I/II trials in humans.

New References (5th Edition)

The following pages add short comments to the papers published since the previous edition (June-October). The comments are from <https://covidreference.com/daily-science>. The complete list of references starts at page 241.

SARS-CoV-2 Vaccine Candidates

Dagotto G, Yu J, Barouch DH. **Approaches and Challenges in SARS-CoV-2 Vaccine Development.** Cell Host Microbe 2020, published 10 August. Full-text: [https://www.cell.com/cell-host-microbe/fulltext/S1931-3128\(20\)30455-8](https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30455-8)

Progress in SARS-CoV-2 vaccine development to date has been faster than for any other pathogen in history. In this perspective, [Dan Barouch](#), [Gabriel Dagotto](#) and [Jingyou Yu](#) discuss three topics that are critical for SARS-CoV-2 vaccine development:

1. Antigen selection and engineering
2. Pre-clinical challenge studies in non-human primate models
3. Immune correlates of protection

Phase 3 vaccine candidates

ChAdOx1 (ASTRAZENECA)

Folegatti PM, Ewer KJ, Aley PK, et al. **Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial.** Lancet. 2020 Aug 15;396(10249):467-478. PubMed: <https://pubmed.gov/32702298>. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31604-4](https://doi.org/10.1016/S0140-6736(20)31604-4)

Andrew Pollard and colleagues report their Phase I/II randomized trial of a chimpanzee adenovirus-vector vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein. Study participants received either ChAdOx1 nCoV-19 (n = 543) or a meningococcal conjugate vaccine (MenACWY) as control (n = 534). In ChAdOx1 vaccinees, T cell responses peaked on day 14, anti-spike IgG responses rose by day 28, and neutralizing antibody responses against SARS-CoV-2 were detected in > 90% (find more details in the paper, especially about results after a booster dose). Adverse events such as fatigue, headache, and local tenderness commonly occurred. There were no serious adverse events.

van Doremalen N, Lambe T, Spencer A, et al. **ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques**. Nature 2020, published 30 July. Full-text: <https://doi.org/10.1038/s41586-020-2608-y>

ChAdOx1 vaccine (see also the [July 20 Top 10](#)) induced a balanced Th1/Th2 humoral and cellular immune response in rhesus macaques. The bad news (for prevention policies in general and for anti-vaxxers in particular): there was no difference in nasal shedding between vaccinated and control animals.

BNT162B1 (PFIZER / BIONTECH)

Mulligan MJ, Lyke KE, Kitchin N, et al. **Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults**. Nature. 2020 Aug 12. PubMed: <https://pubmed.gov/32785213>. Full-text: <https://doi.org/10.1038/s41586-020-2639-4>

Mark Mulligan, Kirsten Lyke, Nicholas Kitchin, Judith Absalon and colleagues report the safety, tolerability, and immunogenicity data from an ongoing study in 45 healthy adults, randomized to receive 2 doses, separated by 21 days, of 10 µg, 30 µg, or 100 µg of **BNT162b1**. BNT162b1, developed by **BioN-Tech** and **Pfizer**, is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD). A clear dose-level response in elicited neutralizing titers was observed after doses 1 and 2 with a particularly steep dose response between the 10 µg and 30 µg dose levels. Geometric mean neutralizing titers reached 1.9- to 4.6-fold that of a panel of COVID-19 convalescent human sera at least 14 days after a positive SARS-CoV-2 PCR. The clinical testing of BNT162b1 is taking place in the context of a broader, ongoing COVID-19 vaccine development program by both companies. That program includes the clinical testing of three additional vaccine candidates, including candidates encoding the full-length spike.

Abbasi J. **COVID-19 and mRNA Vaccines-First Large Test for a New Approach**. JAMA. 2020 Sep 3. PubMed: <https://pubmed.gov/32880613>. Full-text: <https://doi.org/10.1001/jama.2020.16866>

mRNA vaccines like **BNT162b2** from BioNTech and Pfizer and **mRNA-1273** by Moderna have ‘the potential to be truly transformative’ ([Drew Weissman](#)) but have never been tested in large-scale human trials. Now both vaccines have entered Phase III trials, which together will enroll an estimated 60,000 volun-

teers. Follow [Jennifer Abbasi](#) on a tour of ‘proof in the pudding’ and mRNA vaccines beyond COVID-19.

Sahin U, Muik A, Derhovanessian E, et al. **Concurrent human antibody and TH1 type T-cell responses elicited by a COVID-19 RNA vaccine.** medRxiv 2020, posted 20 July. Full-text: <https://doi.org/10.1101/2020.07.17.20140533>

The authors present antibody and T cell responses after BNT162b1 vaccination from a non-randomized open-label Phase I/II trial in healthy adults. BNT162b1 elicited robust CD4+ and CD8+ T cell responses and strong antibody responses, with RBD-binding IgG concentrations clearly above those in a COVID-19 convalescent human serum panel. Most participants had Th1 skewed T cell immune responses with RBD-specific CD8+ and CD4+ T cell expansion. Interferon (IFN) γ was produced by a high fraction of RBD-specific CD8+ and CD4+ T cells.

Nat Biomed Eng (Editors). **Fast-and-fit vaccines.** Nat Biomed Eng 2020, published 10 August 2020. Full-text: <https://doi.org/10.1038/s41551-020-00605-9>

Two mRNA vaccine formulations against COVID-19, one developed by a collaboration between Pfizer and BioNTech, and the other by Moderna and the National Institute of Allergy and Infectious Diseases (NIAID) in the US ([Nat Biomed Eng 2020](#)), have the potential to be truly transformative; however, they have never been tested in large-scale human trials.

RNA-1273 (MODERNA)

Corbett KS, Flynn B, Foulds KE, et al. **Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates.** N Engl J Med 2020b, published 28 July. Full-text: <https://doi.org/10.1056/NEJMoa2024671>

Vaccination of non-human primates with mRNA-1273 induces robust SARS-CoV-2 neutralizing activity, rapid protection in the upper and lower airways, and no pathologic changes in the lung. For this important vaccine trial, Barney Graham, Robert Seder and colleagues divided 12 female and 12 male Indian-origin rhesus macaques into groups of three and vaccinated them intramuscularly at week 0 and at week 4 with either 10 or 100 μ g of mRNA-1273 or placebo. At week 8 (4 weeks after the second vaccination), all animals were challenged with SARS-CoV-2. mRNA-1273 induced antibody levels exceeding those found in human convalescent phase serum. Vaccination also induced type 1 helper T cell (Th1)-biased CD4 T cell responses and low or undetectable Th2 or CD8 T cell responses. No viral replication was detectable in the nose of

any of the eight animals in the 100 µg dose group by day 2 after challenge (8 weeks after the first vaccination). The ability to limit viral replication in both the lower and the upper airways will have important implications for vaccine-induced prevention of both SARS-CoV-2 disease and transmission.

Jackson LA, Anderson EJ, Roupael NG, et al. **An mRNA Vaccine against SARS-CoV-2 - Preliminary Report.** N Engl J Med. 2020 Jul 14. PubMed: <https://pubmed.gov/32663912>. Full-text: <https://doi.org/10.1056/NEJMoa2022483>

This study conducted in Washington and Atlanta evaluated the candidate vaccine mRNA-1273 that encodes the stabilized prefusion SARS-CoV-2 spike protein. In a Phase I open label trial, 45 healthy adults received two vaccinations, 28 days apart, at three different doses. Antibody responses were higher with a higher dose and further increased after the second vaccination, leading to serum-neutralizing activity in all participants. Values were similar to those in the upper half of the distribution of a panel of control convalescent serum specimens. Solicited adverse events that occurred in > 50% included fatigue, chills, headache, myalgia, and pain at the injection site.

CORONAVAC® (SINOVAC)

Gao Q, Bao L, Mao H, et al. **Development of an inactivated vaccine candidate for SARS-CoV-2.** Science. 2020 Jul 3;369(6499):77-81. PubMed: <https://pubmed.gov/32376603>. Full-text: <https://doi.org/10.1126/science.abc1932>

The authors developed a purified inactivated SARS-CoV-2 virus vaccine candidate, which induced SARS-CoV-2-specific neutralizing antibodies in mice, rats, and non-human primates. These antibodies neutralized 10 representative SARS-CoV-2 strains, suggesting a possible broader neutralizing ability against other strains.

CTII-nCoV (CANsino)

Zhu FC, Guan XH, Li YH, et al. **Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial.** Lancet. 2020 Aug 15;396(10249):479-488. PubMed: <https://pubmed.gov/32702299>. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31605-6](https://doi.org/10.1016/S0140-6736(20)31605-6)

Wei Chen and colleagues report results from a randomized Phase II trial of an Ad5-vector COVID-19 vaccine from a single center in Wuhan. More than 90% of participants had T cell responses, seroconversion of binding antibody occurred in more than 96%, and neutralizing antibodies were seen in about 85%. The authors found that compared with the younger population, older people had a significantly lower immune response, but higher tolerability, to the Ad5-vector COVID-19 vaccine. In a Phase IIb trial, an additional dose might therefore be needed to induce a better immune response in an older population. Adverse events such as fever, fatigue, headache, or local site pain were comparable to the ChAdOx1 study above.

SPUTNIK V (GAMALEYA)

Logunov DY, Dolzhikova IV, Zubkova OV, et al. **Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia.** Lancet 2020, published 4 September. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31866-3](https://doi.org/10.1016/S0140-6736(20)31866-3)

It was high time to see some data on an “approved” vaccine. See also the comment by [Naor Bar-Zeev](#) and [Tom Inglesby](#) [Bar-Zeev N, Inglesby T. **COVID-19 vaccines: early success and remaining challenges.** Lancet 2020, published 4 September. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31867-5](https://doi.org/10.1016/S0140-6736(20)31867-5)].

On September 5, we commented that it was high time to see some data on an “approved” vaccine, consisting of two recombinant adenovirus vectors carrying the spike glycoprotein (Sputnik V, presented as the world’s “*premiere*”, like planting a tiny flag in the sea bed two and a half miles beneath the North Pole in 2007).

Bucci E, Andreev, Björkman A, et al. **Safety and efficacy of the Russian COVID-19 vaccine: more information needed.** Lancet September 21, 2020. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31960-7](https://doi.org/10.1016/S0140-6736(20)31960-7)

A few days later, the study received these notes of serious concerns. Dozens of authors raised doubts about the reliability of the data. The main issue (among many others): there were several data patterns which appeared repeatedly for the reported experiments. A Photoshop fake? Enrico Bucci and colleagues conclude that “in lack of the original numerical data, no conclusions can be definitively drawn on the reliability of the data presented, especially regarding the apparent duplications detected”. For more details see also <https://cattiviscienziati.com/2020/09/07/note-of-concern/>

Logunov DY, Dolzhikova IV, Tukhvatullin AI. **Safety and efficacy of the Russian COVID-19 vaccine: more information needed – Authors’ reply**. Lancet September 21, 2020. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31970-X](https://doi.org/10.1016/S0140-6736(20)31970-X)

The author’s reply. They “confirm that individual participant data will be made available on request to DYL and that after approval of a proposal, data can be shared through a secure online platform”. Shall we hold our breath?

SINOPHARM WUHAN

Xia S, Duan K, Zhang Y, et al. **Effect of an Inactivated Vaccine Against SARS-CoV-2 on Safety and Immunogenicity Outcomes: Interim Analysis of 2 Randomized Clinical Trials**. JAMA. 2020 Aug 13:e2015543. PubMed: <https://pubmed.gov/32789505>. Full-text: <https://doi.org/10.1001/jama.2020.15543>

An Pan, Xiaoming Yang and colleagues provide the first interim safety, tolerability, and immune response results for a β -propiolactone-inactivated whole-virus vaccine adjuvanted in 0.5 mg of aluminum hydroxide. The incidence rate of adverse reactions in the current study (15.0% among all participants) was not significantly different between the vaccine groups and the active control (alum) groups; it was also lower compared with results of other SARS-CoV-2 candidate vaccines. The neutralizing antibody response suggested that the inactivated vaccine may effectively induce antibody production, but the optimal interval between injections and times of booster injections of the inactivated vaccine remains unclear. In the discussion, find more about ADE and VAERD. See also the comment by [Mark Mulligan: An Inactivated Virus Candidate Vaccine to Prevent COVID-19](#). JAMA. 2020 Aug 13. PubMed: <https://pubmed.gov/32789500>. Full-text: <https://doi.org/10.1001/jama.2020.15539>

NVX-CoV2373 (NOVAVAX)

Keech C, Albert G, Cho I, et al. **Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine.** N Engl J Med. 2020 Sep 2. PubMed: <https://pubmed.gov/32877576>. Full-text: <https://doi.org/10.1056/NEJMoa2026920>

NVX-CoV2373 is a recombinant SARS-CoV-2 nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant. In 83 participants younger than 60 years of age, two injections of NVX-CoV2373 delivered in the deltoid muscle on day 0 and 21 appeared to be safe. Immune responses exceeded levels in COVID-19 convalescent serum, showing high neutralizing antibody responses and T cells with a predominant Th1 phenotype. Phase II has started.

Ad26.COV2.S (JANSSEN)

Mercado NB, Zahn R, Wegmann F et al. **Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques.** Nature 2020, published 30 July. Full-text: <https://doi.org/10.1038/s41586-020-2607-z>

For global deployment and pandemic control, a vaccine that requires only a single immunization would be optimal. Hanneke Schuitemaker, Dan Barouch and colleagues developed a series of adenovirus serotype 26 (Ad26) vectors encoding different variants of the SARS-CoV-2 spike (S) protein and showed the immunogenicity and protective efficacy of a single dose of Ad26 vector-based vaccines in 52 rhesus macaques. The optimal Ad26 vaccine induced robust neutralizing antibody responses and provided complete or near-complete protection in bronchoalveolar lavage and nasal swabs following SARS-CoV-2 challenge.

The Future of SARS-CoV-2 vaccines**Questions**

Bar-Zeev N, Moss WJ. **Encouraging results from phase 1/2 COVID-19 vaccine trials.** Lancet. 2020 Aug 15;396(10249):448-449. PubMed: <https://pubmed.gov/32702300>. Full-text: [https://doi.org/10.1016/S0140-6736\(20\)31611-1](https://doi.org/10.1016/S0140-6736(20)31611-1)

A comment on the two papers above as well as a list of questions to be addressed by the coming Phase III trials:

- Will a single dose be sufficient in older adults, or is a booster dose required?

- Does longevity of response or rates of waning differ with a two-dose regimen, and does longevity of clinical protection require cell-mediated responses?
- Are there host-specific differences in immunogenicity by age, sex, or ethnicity?
- Do T cell responses correlate with protection irrespective of humoral titers?
- Are there specific adverse events in pregnant women?

Vaccine Approval

FDA 20200630. FDA News Release. **Coronavirus (COVID-19) Update: FDA Takes Action to Help Facilitate Timely Development of Safe, Effective COVID-19 Vaccines.** Published 30 June 2020. Full-text: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-action-help-facilitate-timely-development-safe-effective-covid>

This press release announces [guidance](#) with recommendations for companies and researchers developing COVID-19 vaccines for the purpose of licensure. The guidance describes the agency's current recommendations regarding the data needed to facilitate the manufacturing, clinical development, and approval of a COVID-19 vaccine. It also states that the FDA would expect that a COVID-19 vaccine would prevent disease or decrease its severity in at least 50% of people who are vaccinated.

SETBACKS

Phillips N, Cyranoski D, Mallapathy S. **A leading coronavirus vaccine trial is on hold: scientists react.** Nature News September 9, 2020. Full-text: <https://www.nature.com/articles/d41586-020-02594-w>

This article summarizes what is known about the news of the day: AstraZeneca has reported a case of a transverse myelitis in a person who received AZD1222, an adenoviral-vector vaccine that harnesses a cold-causing 'adenovirus' isolated from chimpanzees. The Phase III trial was "voluntarily paused". However, details of the adverse event, including how serious it was and when it happened, have not been reported. It is still unclear whether the person received the vaccine or placebo. Let's wait for the details.

Shah S, Patel J, Alchaki AR. **Development of Transverse Myelitis after Vaccination. A CDC/FDA Vaccine Adverse Event Reporting System (VAERS) Study, 1985–2017.** *Neurology* April 10, 2018; 90. Abstract: https://n.neurology.org/content/90/15_Supplement/P5.099

In the meantime, you may read this review of 119 cases of transverse myelitis (TM) occurring after vaccination, reported during a period of over 30 years to the FDA. Although the reporting rate of post-vaccination TM was in the range expected in the general population, the unbalanced distribution of these cases in the first 6 weeks after vaccination suggested that the association between vaccination and some cases may not be coincidental. (For antivaxxers: this is rare!)

McAuley AJ, Kuiper MJ, Durr PA, et al. **Experimental and in silico evidence suggests vaccines are unlikely to be affected by D614G mutation in SARS-CoV-2 spike protein.** *npj Vaccines* 5, 96 (2020). <https://doi.org/10.1038/s41541-020-00246-8>

The D614G mutation of the SARS-CoV-2 spike protein has been speculated to adversely affect the efficacy of vaccines. In this article, S. Vasan, Alexander McAuley and colleagues claim that there is no experimental evidence to support this speculation. They performed virus neutralization assays using sera from ferrets that received two doses of the INO-4800 COVID-19 vaccine, and Australian virus isolates (VIC01, SA01 and VIC31) which either possess or lack this mutation.

HUMAN CHALLENGE STUDIES

Callaway E. **Dozens to be deliberately infected with coronavirus in UK ‘human challenge’ trials.** *Nature* 2020, published 20 October. Full-text: <https://www.nature.com/articles/d41586-020-02821-4>

Proponents of the trials say they can be run safely and help to identify effective vaccines, but others have questioned their value.

Cookson C. **UK to test vaccines on volunteers deliberately infected with Covid-19.** *Financial Times* 2020, published 23 September. Full-text: <https://www.ft.com/content/b782f666-6847-4487-986c-56d3f5e46c0b>

In the world’s first COVID-19 ‘human challenge trials’ healthy volunteers will be deliberately infected with SARS-CoV-2 to assess the effectiveness of experimental vaccines.

Jamrozik E, Selgelid MJ. **COVID-19 human challenge studies: ethical issues.** *Lancet Infect Dis.* 2020 May 29:S1473-3099(20)30438-2. PubMed: <https://pubmed.gov/32479747>. Full-text: [https://doi.org/10.1016/S1473-3099\(20\)30438-2](https://doi.org/10.1016/S1473-3099(20)30438-2)

Human challenge studies could accelerate vaccine development, helping to test multiple candidate vaccines. This personal view on ethical issues explains why this will be difficult. The authors argue that human challenge studies can “reasonably be considered ethically acceptable insofar as such studies are accepted internationally and by the communities in which they are done, can realistically be expected to accelerate or improve vaccine development, have considerable potential to directly benefit participants, are designed to limit and minimise risks to participants, and are done with strict infection control measures to limit and reduce third-party risks.”

Deming ME, Michael NL, Robb M, et al. **Accelerating Development of SARS-CoV-2 Vaccines — The Role for Controlled Human Infection Models.** *NEJM* July 1, 2020. Full-text: <https://doi.org/10.1056/NEJMp2020076>. Full-text: <https://www.nejm.org/doi/full/10.1056/NEJMp2020076>

The authors review practical considerations relevant to the development of a SARS-CoV-2 controlled human infection models (CHIMs) and the prerequisites for using such a model. Large, randomized, controlled trials of SARS-CoV-2 vaccines are still the most efficient, generalizable, and scientifically robust path to establishing vaccine efficacy. However, SARS-CoV-2 CHIM development might be able to accelerate the development of later rounds of vaccine candidates.

Kirby T. **COVID-19 human challenge studies in the UK.** *Lancet* October 30, 2020. Full-text: [https://doi.org/10.1016/S2213-2600\(20\)30518-X](https://doi.org/10.1016/S2213-2600(20)30518-X)

Some thoughts about feasibility and ethics of human challenge trials that could potentially accelerate the development of vaccines. The first study phase, which could begin in January 2021, aims to discover the smallest amount of virus it takes to cause the infection in up to 90 healthy young people, aged between 18 and 30 years. The study will probably take place in the high-level isolation unit of the Royal Free Hospital, London, UK. Some commentators have questioned both the timing and the ethical dilemmas presented by the study.

Kahn JP, Henry LM, Mastroianni C, et al. **Opinion: For now, it's unethical to use human challenge studies for SARS-CoV-2 vaccine development.** PNAS October 29, 2020. Full-text: <https://doi.org/10.1073/pnas.2021189117>

Important comment: see title. According to the authors, human challenge studies (HCS) to address SARS-CoV-2 face unacceptable ethics challenges, and, further, undertaking them would do a disservice to the public by undermining already strained confidence in the vaccine development process. Ultimately, the social value of these HCS (in terms of deaths averted) hinges on the premise that people at greatest risk of COVID-19-related mortality will receive a safe and efficacious vaccine sooner than they would without HCS. Read why this will be probably not the case and why HCS would do more harm than good.

PREVIEW

Jeyanathan M, Afkhami S, Smaill F, et al. **Immunological considerations for COVID-19 vaccine strategies.** Nat Rev Immunol 2020, published 4 September. Full-text: <https://doi.org/10.1038/s41577-020-00434-6>

In this review, [Zhou Xing](#), [Mangalakumari Jeyanathan](#) and colleagues describe the immunological principles of SARS-CoV-2 vaccine development and analyze the current vaccine candidates, their strengths and potential shortfalls. They also make inferences about their chances of success. A hazardous undertaking.

Vaccine distribution

Kupferschmidt K. **'Vaccine nationalism' threatens global plan to distribute COVID-19 shots fairly.** Science 2020, 28 July. Full-text: <https://www.sciencemag.org/news/2020/07/vaccine-nationalism-threatens-global-plan-distribute-covid-19-shots-fairly>

'We will not sell it at cost.' (We will sell it for profit.) That was the statement, a few days ago, of a company that is receiving almost [1,000,000,000 dollars from US tax payers](#) for developing a COVID-19 vaccine. Fortunately, other companies, too, are producing vaccines and good old WHO and other international organizations have set up a system to accelerate and equitably distribute vaccines, the COVID-19 Vaccines Global Access ([COVAX](#)) Facility. [Kai Kupferschmidt](#) summarizes the current state-of-affairs.

Callaway E. **The unequal scramble for coronavirus vaccines — by the numbers.** Nature 2020, published 24 August. Full-text: <https://www.nature.com/articles/d41586-020-02450-x>

Will SARS-CoV-2 vaccines be only for the rich? Ellen Callaway shows how wealthy countries have struck deals to buy more than two billion doses of coronavirus vaccine. Find out that the UK is the world's highest *per capita* buyer, with 340 million doses purchased: around 5 doses for each citizen. And read more about COVAX, spearheaded by GAVI, a Geneva-based funder of vaccines for low-income countries, along with CEPI and the World Health Organization. It aims to secure 2 billion doses of vaccines. One billion are for 92 low- and middle-income countries and economies (LMICS), which make up half the world's population.

Schwartz JL. **Evaluating and Deploying Covid-19 Vaccines — The Importance of Transparency, Scientific Integrity, and Public Trust.** N Engl J Med 2020; 383:1703-1705. Full-text: <https://doi.org/10.1056/NEJMp2026393>

The situation in the US is dire, public confidence in vaccination is fragile. Jason Schwartz insists that COVID-19 vaccination programs will succeed only if there is widespread belief that available vaccines are safe and effective and that policies for prioritizing their distribution are equitable and evidence-based. He clearly sees that trust in science and expertise are threatened, as the pandemic has shown with catastrophic results. Listen also to the [audio interview](#) (12:02).

Impact of vaccines on the pandemic

Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KWR, Pollard AJ. **What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2.** Lancet Infect Dis 2020, published 27 October. Full-text: [https://doi.org/10.1016/S1473-3099\(20\)30773-8](https://doi.org/10.1016/S1473-3099(20)30773-8)

A vaccine against SARS-CoV-2 might act against infection, disease, or transmission and a vaccine capable of reducing any of these elements could contribute to disease control. However, the most important efficacy endpoint, protection against severe disease and death, is difficult to assess in Phase III clinical trials. In this review, Susanne Hodgson and colleagues explore the challenges in assessing the efficacy of candidate SARS-CoV-2 vaccines, discuss the caveats needed to interpret reported efficacy endpoints, and provide insight into answering the seemingly simple question, “Does this COVID-19 vac-

cine work?” Remember: the fundamental understanding of the pathogen is still evolving.

Lipsitch M, Dean NE. **Understanding COVID-19 vaccine efficacy**. Science. 2020 Oct 21:eabe5938. PubMed: <https://pubmed.gov/33087460>. Full-text: <https://doi.org/10.1126/science.abe5938>

Marc Lipsitch and Natalie Dean publish the shortest abstract in months: “Vaccine efficacy in high-risk groups and reduced viral shedding are important for protection.” Explore strategic prioritization plans.

Immunization Fundamentals

Passive immunization against SARS-CoV-2

CONVALESCENT PLASMA

Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P; PLACID Trial Collaborators. **Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial)**. BMJ. 2020 Oct 22;371:m3939. PubMed: <https://pubmed.gov/33093056>. Full-text: <https://doi.org/10.1136/bmj.m3939>

Convalescent plasma (CP; giving neutralizing antibodies of people who made it through SARS-CoV-2 infection) has been one of the biggest hopes. This open label randomized controlled trial (RCT; the largest to date with results) investigated the effectiveness of CP in adults with moderate COVID-19 in 39 public and private hospitals across India. In total, 235 patients were assigned to two doses of 200 mL CP and 229 to standard of care only (control arm). Progression to severe disease or all-cause mortality at 28 days after enrolment occurred in 44 (19%) participants receiving CP and in 41 (18%) in the control arm. Moreover, CP treatment did not show anti-inflammatory properties and there was no difference between patients with or without neutralizing antibodies at baseline (who had produced their own antibodies or not). The main limitation: the authors did not measure the antibody titers in CP before transfusion because validated, reliable commercial tests were not available when the trial started. Let’s hope that low antibody titers were the reason for the lack of efficacy.

Pathak EB. **Convalescent plasma is ineffective for covid-19**. BMJ. 2020 Oct 22;371:m4072. PubMed: <https://pubmed.gov/33093025>. Full-text: <https://doi.org/10.1136/bmj.m4072>

A strong statement, after all (and some thoughts on how to deal with the bad results of the PLACID trial).

MONOCLONAL ANTIBODIES

Cohen J. **Designer antibodies could battle COVID-19 before vaccines arrive**. Science 2020, published 4 August. Full-text: <https://www.sciencemag.org/news/2020/08/designer-antibodies-could-battle-covid-19-vaccines-arrive>

Science writer [Jon Cohen](#) describes how the competition is heating up to produce targeted monoclonal antibodies which could both prevent and treat COVID-19. Read about treatment and prevention trials, antibody cocktails and the role monoclonal antibodies might play even after the general availability of effective vaccines. Read also about the final problem of monoclonal antibodies: their cost, especially for the higher doses needed for treatment. Don't expect monoclonals to be affordable globally. Rather, they might split the world into the haves and have-nots, like many previous drugs. Another reason why accessible vaccines are so important!

Ledford H. **Antibody therapies could be a bridge to a coronavirus vaccine — but will the world benefit?** Nature 2020, published 11 August. Full-text: <https://www.nature.com/articles/d41586-020-02360-y>

Are monoclonal antibodies a bridging solution before the general availability of a vaccine? [Heidi Lenford](#) reminds us that monoclonals are complex and expensive to produce, leaving people from poor countries locked out.

Ledford H. **The race to make COVID antibody therapies cheaper and more potent**. Nature 2020, published 23 October. Full-text: <https://www.nature.com/articles/d41586-020-02965-3>

Injections of antibodies might prevent mild COVID-19 from becoming severe, but the treatments are expensive and difficult to make.

Hansen J, Baum A, Pascal KE, et al. **Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail.** Science. 2020 Aug 21;369(6506):1010-1014. PubMed: <https://pubmed.gov/32540901>. Full-text: <https://doi.org/10.1126/science.abd0827>

Researchers from Regeneron generated a large panel of antibodies against the spike protein from humanized mice and from three recovered patients. From this panel, approximately 40 antibodies with distinct sequences and potent neutralization activities were chosen for additional characterization, including antibody pairs that do not compete for binding to the receptor binding domain (RBD). REGN10987 and REGN10933 represent such a pair of antibodies: REGN10933 binds at the top of the RBD, extensively overlapping the binding site for ACE2. The epitope for REGN10987 is located on the side of the RBD, away from the REGN10933 epitope, and has little to no overlap with the ACE2 binding site.

Baum A, Fulton BO, Wloga E, et al. **Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies.** Science. 2020 Aug 21;369(6506):1014-1018. PubMed: <https://pubmed.gov/32540904>. Full-text: <https://doi.org/10.1126/science.abd0831>

Proof of principle in a cell model, using vesicular stomatitis virus pseudoparticles expressing the SARS-CoV-2 spike protein. Simultaneous treatment with REGN10933 and REGN10987 precluded the appearance of escape mutants. Thus, this cocktail did not rapidly select for mutants, presumably because escape would require the unlikely occurrence of simultaneous viral mutation at two distinct genetic sites, so as to ablate binding and neutralization by both antibodies in the cocktail.

Baum A, Ajithdoss D, Copin R, et al. **REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters.** Science 2020b, published 9 October. Full-txt: <https://doi.org/10.1126/science.abe2402>

The authors evaluate REGN-COV2, a cocktail of two neutralizing antibodies (REGN10987+REGN10933) targeting non-overlapping epitopes on the SARS-CoV-2 spike protein, in rhesus macaques and golden hamsters. REGN-COV2 can reduce virus load and decrease virus-induced pathological sequelae in rhesus macaques. In hamsters, the cocktail limited weight loss and evidence of pneumonia in the lungs. It is too early to predict the clinical usefulness of this cocktail in COVID-19 patients. It is currently being tested in clinical trials.

Hunting for antibodies to combat COVID-19. Biopharma dealmakers 2020, published 1 September. Full-text: <https://www.nature.com/articles/d43747-020-01115-y>

The development of highly successful monoclonal antibody-based therapies for cancer and immune disorders has created a wealth of expertise and manufacturing capabilities. Is there room for monoclonals for prevention or treatment of severe COVID-19 before the general availability of vaccines and efficient antiviral drugs? Find out how the 'COVID-19 antibody sphere' (Amgen, AstraZeneca, Vir, Regeneron, Lilly, Adagio) is building partnerships.

Active immunization against SARS-CoV-2

SARS-CoV-2 vaccine platforms

Martin C, Lowery D. **mRNA vaccines: intellectual property landscape.** Nat Rev Drug Discov 2020, 27 July. Full-text: <https://www.nature.com/articles/d41573-020-00119-8>

Overall filing activity aims at protecting methods to improve mRNA delivery efficiency as well as pharmacological modifications to reduce mRNA instability and innate immunogenicity. Moderna, CureVac, BioNTech and GSK own nearly half of the mRNA vaccine patent applications in the world.

Questions for the Future

Longevity of the immunological memory against SARS-CoV-2

Wajnberg A, Amanat F, Firpo A, et al. **Robust neutralizing antibodies to SARS-CoV-2 infection persist for months.** Science 2020, published 28 October. Full-text: <https://doi.org/10.1126/science.abd7728>

Assessing the antibody response to SARS-CoV-2 infection in mild and asymptomatic cases is of high importance since they constitute the majority of infections. Now, Ania Wajnberg, Florian Krammer, Carlos Cordon-Cardo and colleagues show that the vast majority of infected individuals with mild-to-moderate COVID-19 experience had robust IgG antibody responses against the viral spike protein. The authors from Icahn School of Medicine at Mount Sinai, New York, analyzed a dataset of 30,082 individuals. Titers were relatively stable for at least a period approximating 5 months. Anti-spike binding titers correlated with neutralization of authentic SARS-CoV-2. The data suggests that more than 90% of seroconverters make detectable neutralizing antibody responses.

Gudbjartsson DF, Norddahl GL, Melsted P, et al. **Humoral Immune Response to SARS-CoV-2 in Iceland.** N Engl J Med 2020, published 1 September. Full-text: <https://doi.org/10.1056/NEJMoa2026116>

How long will people be protected from reinfection by SARS-CoV-2? Generally, many months, as may be expected from a coronavirus infection. In this study by Kari Stefansson, Daniel Gudbjartsson and colleagues, over 90% of 1215 qPCR-positive persons tested positive with two pan-Ig SARS-CoV-2 antibody assays and remained seropositive 120 days after diagnosis, with no decrease of antibody levels. Another piece of good news: the infection fatality risk in Iceland was 0.3%. Less good news: only 0.9% of Icelanders were infected with SARS-CoV-2 indicating that the Icelandic population is vulnerable to a second wave of infection.

See also the editorial by Galit Alter and Robert Seder: Alter G, Seder R: **The Power of Antibody-Based Surveillance.** N Engl J Med 2020, published 1 September. Full-text: <https://doi.org/10.1056/NEJMe2028079>. In particular, they stress the utility of antibody assays as highly cost-effective alternatives to PCR testing for population-level surveillance, which is critical to the safe reopening of cities and schools.

Ibarrondo FJ, Fulcher JA, Goodman-Meza D, et al. **Rapid Decay of Anti-SARS-CoV-2 Antibodies in Persons with Mild Covid-19.** N Engl J Med. 2020 Sep 10;383(11):1085-1087. PubMed: <https://pubmed.gov/32706954>. Full-text: <https://doi.org/10.1056/NEJMc2025179>

Comments:

Bölke E, Matuschek C, Fischer JC. **Loss of Anti-SARS-CoV-2 Antibodies in Mild Covid-19.** N Engl J Med. 2020 Oct 22;383(17):1694-1695. PubMed: <https://pubmed.gov/32966710>. Full-text: <https://doi.org/10.1056/NEJMc2027051>

Terpos E, Mentis A, Dimopoulos MA. **Loss of Anti-SARS-CoV-2 Antibodies in Mild Covid-19.** N Engl J Med. 2020 Oct 22;383(17):1695. PubMed: <https://pubmed.gov/32966711>. Full-text: <https://doi.org/10.1056/NEJMc2027051>

Kutsuna S, Asai Y, Matsunaga A. **Loss of Anti-SARS-CoV-2 Antibodies in Mild Covid-19.** N Engl J Med. 2020 Oct 22;383(17):1695-1696. PubMed: <https://pubmed.gov/32966712>. Full-text: <https://doi.org/10.1056/NEJMc2027051>

The controversy about anti-SARS-CoV-2 antibody decay continues. Some groups found a marked decline while others obtained conflicting results that suggest stability over time.

Seow J, Graham C, Merrick B, et al. **Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans.** Nat Microbiol (2020). Full-text: <https://doi.org/10.1038/s41564-020-00813-8>

Antibody responses to SARS-CoV-2 can be detected in most infected individuals 10–15 d after the onset of COVID-19 symptoms. But how long will antibody responses be maintained, and will they provide protection from reinfection? To answer these questions, Katie Doores, Jeffrey Seow and colleagues collected sequential serum samples up to 94 d post onset of symptoms from 65 individuals with SARS-CoV-2 infection. They show that the kinetics of the neutralizing antibody response to SARS-CoV-2 is typical of an acute viral infection where a peak response is detected 3–4 weeks post-infection, which then wanes. Their results suggest that for individuals who develop a low neutralizing antibody response (ID_{50} 100–300), titers can return to baseline over a relatively short period, whereas those who develop a robust neutralizing antibody response maintain titers $> 1,000$ despite the initial decline. Should we already reconsider widespread serological testing and antibody protection against reinfection with SARS-CoV-2? The authors conclude that vaccine boosters might be required to provide long-lasting protection.

Pre-existing immune responses against SARS-CoV-2

Posten D, Weisblum Y, Wise H, et al. **Absence of SARS-CoV-2 neutralizing activity in pre-pandemic sera from individuals with recent seasonal coronavirus infection.** medRxiv 2020, published 11 October. Full-text: <https://doi.org/10.1101/2020.10.08.20209650>

Bad news from Rockefeller University. Paul Bieniasz, Daniel Poston and colleagues measured neutralizing activity against SARS-CoV-2 in pre-pandemic sera from patients with prior PCR-confirmed seasonal coronavirus infection. While neutralizing activity against seasonal coronaviruses was detected in nearly all sera, cross-reactive neutralizing activity against SARS-CoV-2 was undetectable. The authors conclude that while it is possible that there are rare instances of individuals possessing antibodies from prior seasonal HCoV infection may be able to also target SARS-CoV-2 S, their data would argue against a broad role for pre-existing protective humoral immunity against SARS-CoV-2. These findings have not yet been peer reviewed.

Outlook

VACCINE SKEPTICISM

Burki T. **The online anti-vaccine movement in the age of COVID-19.** *Lancet Digit Health.* 2020 Oct;2(10):e504-e505. PubMed: <https://pubmed.gov/32984795>. Full-text: [https://doi.org/10.1016/S2589-7500\(20\)30227-2](https://doi.org/10.1016/S2589-7500(20)30227-2)

About 31 million people follow anti-vaccine groups on Facebook, with 17 million people subscribing to similar accounts on YouTube. Within a decade, the anti-vaccination movement could overwhelm pro-vaccination voices online. If that came to pass, the consequences would stretch far beyond COVID-19. This article discusses some strategies.

SPEED

Slaoui M, Hepburn M. **Developing Safe and Effective Covid Vaccines — Operation Warp Speed's Strategy and Approach.** *N Engl J Med* 2020, published 26 August. Full-text: <https://doi.org/10.1056/NEJMp2027405>

What is OWS and what does it do? Moncef Slaoui and Matthew Hepburn from Operation Warp Speed explain the forces behind a national vaccine strategy. The players: Pfizer and BioNTech, AstraZeneca and Oxford University, Janssen, Moderna, Janssen, Novavax, Sanofi/GSK. Will they succeed in this unprecedented endeavor?

Arnold C. **How computational immunology changed the face of COVID-19 vaccine development.** *Nat Med.* 2020 Jul 15. PubMed: <https://pubmed.gov/32669667>. Full-text: <https://doi.org/10.1038/d41591-020-00027-9>

After more than two decades of work, computational immunology now enables the development of a candidate vaccine in just a few hours. However, no *in silico* analysis, no matter how high-quality the input and how exacting the computational algorithms, will ever be a substitute for experimental data.

Corbett KS, Edwards DK, Leist SR et al. **SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness.** *Nature* 2020, published 5 August. Full-text: <https://doi.org/10.1038/s41586-020-2622-0>

The authors provide a paradigm for rapid vaccine development: a generalizable vaccine solution for *Betacoronavirus* and a commercial mRNA vaccine de-

livery platform; a vaccine development programme initiated on the basis of pathogen sequences alone; a proof of concept for the prototype-pathogen approach to pandemic preparedness and response that is predicated on identifying generalizable solutions for medical countermeasures within virus families or genera. The authors anticipate a huge potential for future vaccine research: “There are 24 other virus families that are known to infect humans, and sustained investigation of those potential threats will improve our readiness for future pandemics.”

Price WN 2nd, Rai AK, Minssen T. **Knowledge transfer for large-scale vaccine manufacturing.** Science. 2020 Aug 21;369(6506):912-914. PubMed: <https://pubmed.gov/32792464>. Full-text: <https://doi.org/10.1126/science.abc9588>

Identifying an effective SARS-CoV-2 vaccine and prove its safety in huge clinical trials is only the first step. The next step is not less challenging: manufacturing vaccines at enormous scale. In this Policy Forum, law school scholars [Nicholson Price](#), [Arti Rai](#) and [Timo Minssen](#) explain that fast manufacturing will require not only physical capacity but also access to knowledge not contained in patents or in other public disclosures. Follow the authors on a path through the jungle of licenses, know-how transfer, hostage taking and manufacturing secrecy, and discover why large biopharmaceutical firms are now willing to share information that they might previously have viewed as providing competitive advantage.

COMPREHENSIVE VACCINE TESTING

Helfland BK, Webb M, Gartaganis SL, et al. **The Exclusion of Older Persons From Vaccine and Treatment Trials for Coronavirus Disease 2019—Missing the Target.** JAMA Intern Med, September 28, 2020. Full-text: <https://doi.org/10.1001/jamainternmed.2020.5084>

Those most in need are excluded: in this important review, Benjamin Helfland and colleagues analyzed clinical COVID-19 trials for age exclusions. In 232 Phase III clinical trials, 38 included age cut-offs and 77 had exclusions preferentially affecting older adults. Of 18 vaccine trials, 11 included age cut-offs, and the remaining 7 had broad non-specified exclusions. These findings indicate that older adults are likely to be excluded from more than 50% of COVID-19 clinical trials and 100% of vaccine trials. Why? Such exclusion will limit the ability to evaluate the efficacy, dosage, and adverse effects of the intended treatments.

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6. Diagnostic Tests and Procedures

Christian Hoffmann

Diagnosis

Rapid identification and isolation of infected individuals is crucial. Diagnosis is made using clinical, laboratory and radiological features. As symptoms and radiological findings of COVID-19 are non-specific, SARS-CoV-2 infection has to be confirmed by nucleic acid-based polymerase chain reaction (PCR), amplifying a specific genetic sequence in the virus. Within just a few days after the first cases were published, a validated diagnostic workflow for SARS-CoV-2 was presented ([Corman 2020](#)), demonstrating the enormous response capacity achieved through coordination of academic and public laboratories in national and European research networks.

There is an interim guidance for diagnostic testing for COVID-19 in suspected human cases, published by WHO in March and updated on September 11, 2020 ([WHO 20200911](#)). Several comprehensive up-to-date reviews of laboratory techniques in diagnosing SARS-CoV-2 have been published recently ([Kilic 2020](#), [Loeffelholz 2020](#)).

According to WHO, the decision to test “should be based on both clinical and epidemiological factors”, in order to support clinical management of patients and infection control measures. In symptomatic patients, a PCR test should be immediately carried out, especially for medical professionals with symptoms. In particular, this applies to nursing homes and other long-term facilities where large outbreaks with high resident mortality may occur. In these settings, every day counts: both residents and health-care workers should be tested immediately. In regression analyses among 88 nursing homes with a documented case before facility-wide testing occurred, each additional day between identification of the first case and completion of facility-wide testing was associated with identification of 1.3 additional cases ([Hatfield 2020](#)). However, the predictive value of the tests markedly varies with time from exposure and symptom onset. The false-negative rate is lowest 3 days after onset of symptoms, or approximately 8 days after exposure (see below).

In settings with limited resources, however, patients should only be tested if a positive test results in imperative action. It does not necessarily make sense to attempt to ascertain the prevalence of infection by PCR. For example, in a family which was put on quarantine after the infection was confirmed in one

member, not all household contacts have to be tested, especially younger persons with only mild symptoms.

For many countries and regions, there are constantly updated recommendations by authorities and institutions about who should be tested by whom and when: these recommendations are constantly changing and have to be adapted to the local epidemiological situation. The lower the infection rates and the higher the testing capacities, the more patients will be able to be tested.

Specimen collection

Respiratory tract

SARS-CoV-2 can be detected in a wide range of different tissues and body fluids. In a study on 1,070 specimens collected from 205 patients with COVID-19 (Wang X 2020), bronchoalveolar lavage fluid specimens showed the highest positive rates (14 of 15; 93%), followed by sputum (72 of 104; 72%), nasal swabs (5 of 8; 63%), fibrobronchoscopy brush biopsy (6 of 13; 46%), pharyngeal swabs (126 of 398; 32%), feces (44 of 153; 29%), and blood (3 of 307; 1%).

Though respiratory secretions may be quite variable in composition, respiratory samples remain the sample type of choice for diagnostics. Viral replication of SARS-CoV-2 is very high in upper respiratory tract tissues which is in contrast to SARS-CoV (Wolfel 2020). According to WHO, respiratory material for PCR should be collected from upper respiratory specimens (nasopharyngeal and oropharyngeal swab or wash) in ambulatory patients (WHO 2020). It is preferred to collect specimens from both nasopharyngeal and oropharyngeal swabs which can be combined in the same tube. Besides nasopharyngeal swabs, samples can be taken from sputum (if producible), endotracheal aspirate, or bronchoalveolar lavage. It is likely that lower respiratory samples are more sensitive than nasopharyngeal swabs. Especially in seriously ill patients, there is often more virus in the lower than in the upper respiratory tract (Huang 2020). However, there is always a high risk of “aerosolization” and thus the risk that staff members become infected.

A prospective study in two regional hospitals in Hong Kong examined 563 serial samples collected during the viral shedding period of 50 patients: 150 deep throat saliva (DTS), 309 pooled nasopharyngeal (NP) and throat swabs, and 104 sputum (instructions for deep throat saliva: first clear your throat by gargling with your own saliva, and then spit out the DTS into a sterile bottle). Deep throat saliva produced the lowest viral RNA concentration and a lower RT-PCR positive rate compared to conventional respiratory specimens. Buccal swabs do not work well either. In 11 children positive via nasopharyngeal

swabs, 2 remained negative via buccal swabs. There was a general trend for buccal specimens to contain lower SARS-CoV-2 viral loads compared with nasopharyngeal specimens (Kam 2020).

Nasopharyngeal swabs – practical issues

It is important to carry out the swab process correctly. Both nasopharynx and oropharyngeal swabs have a number of error options that all can lead to false negative results. In addition, protective measures must be taken in order not to endanger the examiner. Every swab carries a high risk of infection! Respiratory protection, protective glasses, gowns and gloves are required. The correct putting on and taking off of protective clothing should be practiced! Many mistakes occur even just removing the protective mask. Gathering specimens from nasopharyngeal and throat swabs can cause discomfort for patients and put health-care workers at risk. If not performed properly or in patients with complex and delicate anatomy, there is a risk for adverse events such as cerebrospinal fluid leak (Sullivan 2020). There is a very useful video on protection, preparation, equipment, handling, removing personal protective equipment, etc (Marty 2020).

For the smear, the patient should sit on a chair and put his head slightly back. The examiner should stand at a slightly offset position in order to avoid any possible cough droplet. Tell the patient that it might be uncomfortable for a short time. Swabs should be used that are suitable for virus detection and have the most flexible plastic shaft possible. Wooden sticks can inactivate viruses and pose a high risk of injury. The swab should be held between thumb and forefinger, like a pencil, so the end should not touch anything. The posterior wall of the nasopharynx is often reached after 5-7 cm, indicated by a slight resistance. Mid-turbinate nasal swabs may be less sensitive (Pinninti 2020). Touching the teeth and tongue should be avoided when taking a throat swab; the swab should be removed from the back wall, directly next to the uvula. Caution with the gag reflex! There is a wealth of practical videos on the internet for the correct execution of the swab process.

In order to minimize the exposure risk to health care workers and depletion of personal protective equipment, we have established swab instructions for patients who are able to do this (ie, most of them!) at home. After appropriate instruction, they can perform the swabs themselves. A courier with the tubes is sent directly to the patient's home, and the courier places the tubes at the door. Direct contact between patient and courier should be avoided. The swab tubes should not be touched by the courier (either put them directly in a bag or collect them with an inverted bag) and should be brought back directly (no mailing!). This requires prior, precise instruction, but is usually quite feasible.

Unsupervised home swab collection was comparable to clinician-collected nasopharyngeal swab collection (McCulloch 2020). In one of the largest studies to date, a total of 530 patients with upper respiratory infection were provided with instructions and asked to collect tongue, nasal, and mid-turbinate samples (Tu 2020). A nasopharyngeal sample was then collected from the patient by a healthcare worker. When this NP sample was used as the comparator, the estimated sensitivities of the tongue, nasal, and mid-turbinate samples collected by the patients were 89.8%, 94.0% and 96.2%, respectively.

The swabs can be stored dry or in a small amount of NaCl solution; if necessary, this should be clarified with the laboratory beforehand. Quick PCR examination is important, preferably on the same day if possible. Heat and longer storage can lead to false negative results (Pan 2020).

Lower respiratory specimens may include sputum (if produced) and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory disease. However, a high risk of aerosolization should be considered (adhere strictly to infection prevention and control procedures). Additional clinical specimens may be collected as COVID-19 virus has been detected in blood and stools (see below).

In contrast to many respiratory viruses, SARS-CoV-2 is present in saliva and several studies have shown that posterior oropharyngeal (deep throat) saliva samples are feasible and more acceptable to patients and healthcare workers (To 2020, Yu 2020, Wyllie 2020, Yokota 2020). In a large study on “enhanced” saliva specimens (strong sniff, elicited cough, and collection of saliva/secretions) from 216 patients with symptoms deemed consistent with COVID-19, there was a 100% positive agreement (38/38 positive specimens) and 99.4% negative agreement (177/178 negative specimens).

Fecal shedding

Although no cases of transmission via fecal-oral route have yet been reported, there is also evidence that SARS-CoV-2 is actively replicating in the gastrointestinal tract. Several studies showed prolonged presence of SARS-CoV-2 viral RNA in fecal samples (Chen 2020, Wu 2020). Combining results of 26 studies, a rapid review revealed that 54% of those patients tested for fecal RNA were positive. Duration of fecal viral shedding ranged from 1 to 33 days after a negative nasopharyngeal swab (Gupta 2020). In another meta-analysis of 17 studies, the pooled detection rate of fecal SARS-CoV-2 RNA was 44% and 34% by patient and number of specimens, respectively. Patients who presented with gastrointestinal symptoms (77% vs. 58%) or with a more severe disease (68% vs. 35%) tended to have a higher detection rate.

These studies have raised concerns about whether patients with negative pharyngeal swabs are truly virus-free, or sampling of additional body sites is needed. However, the clinical relevance of these findings remains unclear and there is one study that did not detect infectious virus from stool samples, despite having high virus RNA concentrations (Wolfel 2020). Therefore, the presence of nucleic acid alone cannot be used to define viral shedding or infection potential (Atkinson 2020). For many viral diseases including SARS-CoV or MERS-CoV, it is well known that viral RNA can be detected long after the disappearance of infectious virus.

Specimens other than respiratory and gastrointestinal: blood, urine, breast milk

- Blood – in patients with mild or moderate disease, SARS-CoV-2 is relatively rarely detected in blood (Wang W 2020, Wolfel 2020). In a screening study of 7,425 blood donations in Wuhan, plasma samples were found positive for viral RNA from 2 asymptomatic donors (Chang 2020). Another study from Korea found seven asymptomatic blood donors who were later identified as COVID-19 confirmed cases. None of 9 recipients of platelets or red blood cell transfusions tested positive for SARS-CoV-2 RNA. Transfusion transmission of SARS-CoV-2 was considered to be unlikely (Kwon 2020). As with feces, it remains unclear whether detectable RNA in the blood signifies infectivity. In a study of 167 hospitalized patients, SARS-CoV-2 was found in 64 patients at hospital admission, 3 of 106 serum PCR negative patients and 15 of 61 positive patients died (Hagman 2020). However, the clinical significance of SARS-CoV-2 “RNAemia” needs to be defined.
- Urine – None of 72 urine specimens tested positive (Wang X 2020).
- Breast milk – in a case report, SARS-CoV-2 RNA was detected in breast milk samples from an infected mother on 4 consecutive days. Detection of viral RNA in milk coincided with mild COVID-19 symptoms and a SARS-CoV-2 positive diagnostic test of the newborn (Groß 2020). However, this seems to be rare. Among 64 breast milk samples from 18 infected women, SARS-CoV-2 RNA was detected in only one milk sample; the viral culture for that sample was negative. These data suggest that SARS-CoV-2 RNA does not represent replication-competent virus and that breast milk may not be a source of infection for the infant (Chambers 2020. Case reports of transmitted antibodies in breast milk have also been reported (Dong 2020).

- Vaginal fluid - all samples of 10 women with COVID-19 were negative (Saito 2020).
- Semen – Absence of virus in samples collected from 12 patients in their recovery phase (Song 2020).
- Tears and conjunctival secretions - among 40 patients (10 with conjunctivitis) who tested positive by RT-PCR of nasopharyngeal and oropharyngeal swabs, conjunctival swab PCR was positive for 3 patients, among them one with conjunctivitis (Atum 2020).

PCR

Dozens of in-house and commercial rRT-PCR assays are available as labs worldwide have customized their PCR tests for SARS-CoV-2, using different primers targeting different sections of the virus's genetic sequence. A review of different assays and diagnostic devices was recently published (Loeffelholz 2020). A protocol for real-time (RT)-PCR assays for the detection of SARS-CoV-2 for two RdRp targets (IP2 and IP4) is described at https://www.who.int/docs/default-source/coronaviruse/real-time-rt-pcr-assays-for-the-detection-of-sars-cov-2-institut-pasteur-paris.pdf?sfvrsn=3662fcb6_2

Novel real-time RT-PCR assays targeting the RNA-dependent RNA polymerase (RdRp)/helicase, spike and nucleocapsid genes of SARS-CoV-2 may help to improve the laboratory diagnosis of COVID-19. Compared to the reported RdRp-P2 assay which is used in most European laboratories, these assays do not cross-react with SARS-CoV in cell culture and may be more sensitive and specific (Chan JF 2020).

The limits of detection of commercial kits may differ substantially. However, most comparative studies have shown a high sensitivity and their suitability for screening purposes worldwide:

- In a comparison of 11 different RT-PCR test systems used in seven labs in Germany in March 2020, the majority of RT-PCR assays detected ca 5 RNA copies per reaction (Münchhoff 2020). A reduced sensitivity was noted for the original Charité RdRp gene confirmatory protocol, which may have impacted the confirmation of some cases in the early weeks of the pandemic. The CDC N1 primer/probe set was sensitive and robust for detection of SARS-CoV-2 in nucleic acid extracts from respiratory material, stool and serum from COVID-19 patients.
- Analytical limits of detection for seven SARS-CoV-2 assays using serial dilutions of pooled patient material quantified with droplet digital PCR.

Limits of detection ranged from ≤ 10 to 74 copies/ml for commercial high-throughput laboratory analyzers (Roche cobas, Abbott m2000, and Hologic Panther Fusion) and 167 to 511 copies/ml for sample-to-answer (DiaSorin Simplexa, GenMark ePlex) and point-of-care instruments (Abbott ID NOW) (Fung 2020).

- A total of 239 specimens (168 contained SARS-CoV-2) were tested by five test methods (Procop 2020). The assays that lacked a nucleic acid extraction step produced more false-negative reactions than assays that included this step. The false-negative rates were 0% for the CDC 2019 nCoV Real-Time RT-PCR Diagnostic Panel, 3.5% for TIB MOLBIOL Assay (Roche), 2.4% for Xpert Xpress SARS-CoV-2 (Cepheid), 11.9% for Simplexa COVID-19 Direct Kit (DiaSorin), and 16.7% for the ID NOW COVID-19 (Abbott). Most false negatives were seen in patients with low viral loads.

Qualitative PCR

A qualitative PCR (“positive or negative”) is usually sufficient in routine diagnostics. Quantification of viral RNA is currently (still) only of academic interest.

False positive results are very rare. However, they do occur. Though the analytical specificity of these tests is usually 100%, the clinical specificity is less, due to contamination (a significant problem for NAT procedures) and/or human error in the handling of samples or data (very hard to eliminate entirely). As seen with serology (see below), these false positive results can have substantial effects when prevalence is low (Andrew Cohen, personal communication).

Another problem of any qualitative PCR is false negative results which can have many causes (review: Woloshin 2020). Incorrect smears are particularly common, but laboratory errors also occur. In a review of 7 studies with a total of 1,330 respiratory samples, the authors estimated the false-negative rate of RT-PCR by day since infection. Over the 4 days before symptom onset, the rate decreased from 100% to 67%. On the day of symptom onset (day 5), the rate was 38%, decreasing to 20% (day 8) and then beginning to increase again from 21% (day 9) to 66% (day 21). If clinical suspicion is high, infection should not be ruled out on the basis of RT-PCR alone. The false-negative rate is lowest 3 days after onset of symptoms, or approximately 8 days after exposure (Kucirka 2020). Figure 1 illustrates PCR and antibody detection during SARS-CoV-2 infection.

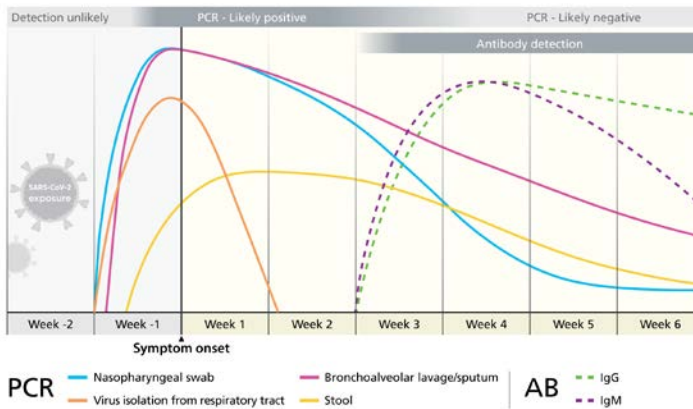


Figure 1. Timeline of diagnostic markers for detection of SARS-CoV-2. AB = Antibody.

Do we need to re-test in the case of a negative PCR? Several studies argue against this strategy, finding very low rates of negative-to-positive conversion with repeated testing (Lepak 2020). Among 20,912 patients, one study analyzed the frequency of SARS-CoV-2 RT-PCR test discordance among individuals initially testing negative by nasopharyngeal swab who were retested on clinical grounds within 7 days. The frequency of subsequent positivity within this window was only 3.5% and similar across institutions (Long 2020). It appears that if the first PCR is negative, a second PCR only yields a small number of positive results.

Several studies have shown that asymptomatic patients also have positive PCR results and can transmit the virus (Bai 2020, Cereda 2020, Rothe 2020). The cycle threshold values of RT-PCR for SARS-CoV-2 (“viral load”) in asymptomatic patients are similar to those in symptomatic patients (Lee S 2020, Lavezzo 2020).

In symptomatic patients, viral shedding may begin 2 to 3 days before the appearance of the first symptoms. Analyzing a total of 414 throat swabs in 94 patients, the highest viral load in throat swabs was found at the time of symptom onset. Infectiousness started from 2.3 days (95% CI, 0.8–3.0 days) before symptom onset and peaked at 0.7 days before symptom onset (He 2020). Infectiousness was estimated to decline quickly within 7 days.

In a cohort of 113 symptomatic patients, the median duration of detection of SARS-CoV-2 RNA was 17 days (interquartiles 13–22 days), measured from the onset of the disease. In some patients, PCR was positive even longer: male gender and a severe course (invasive mechanical ventilation) were independent risk factors for prolonged shedding (Xu K 2020).

Several reports from patients have repeatedly gained much media attraction, showing positive results after repeated negative PCR and clinical recovery (Lan 2020, Xiao AT 2020, Yuan 2020). These studies have raised the question of re-activation or re-infection of COVID-19 (see below, chapter *Clinical Presentation*, page 279). However, it seems probable that the results are much more likely due to methodological problems (Li 2020). At low virus levels, especially during the final days of infection, the viral load can fluctuate and sometimes be detectable, sometimes not (Wolfel 2020). Reactivation, and also a rapid reinfection would be very unusual for coronaviruses.

Quantification of viral load

Several studies have evaluated the SARS-CoV-2 viral load in different specimens. In a small prospective study, the viral load in nasal and throat swabs obtained from 17 symptomatic patients was analyzed in relation to day-of-onset of any symptoms (Zou 2020). Of note, the viral load detected in asymptomatic patients was similar to that in symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients.

In another study on 82 infected individuals, the viral loads in throat swab and sputum samples peaked at around 5–6 days after symptom onset, ranging from around 79,900 copies/ml in the throat to 752,000 copies per mL in sputum (Pan 2020). In a study on oropharyngeal saliva samples, unlike SARS, patients with COVID-19 had the highest viral load near presentation, which could account for the fast-spreading nature of this epidemic (To 2020). The median viral load in posterior oropharyngeal saliva or other respiratory specimens at presentation was $5.2 \log_{10}$ copies per mL (IQR 4.1–7.0) in this study. In a total of 323 samples from 76 patients, the average viral load in sputum (17,429 copies/test) was significantly higher than in throat swabs (2,552 copies) and nasal swabs (651 copies). Viral load was higher in the early and progressive stages than in the recovery stage (Yu 2020). According to a recently published study, viral shedding may already begin 2–3 days before the appearance of the first symptoms and the infectiousness profile may more closely resemble that of influenza than of SARS (He 2020).

Higher viral loads might be associated with severe clinical outcomes. In a large cohort ($n = 1145$) of hospitalized, symptomatic patients from New York, viral loads were measured. In a Cox proportional hazards model adjusting for several confounders, there was a significant independent association between viral load and mortality (hazard ratio 1.07, 95% CI 1.03–1.11, $p = 0.0014$), with a 7% increase in hazard for each log transformed copy/mL (Pujadas 2020).

However, prospective trials are needed to evaluate the role of SARS-CoV-2 viral load as a marker for assessing disease severity and prognosis.

Should we measure viral load? Probably yes. It may be helpful in clinical practice. A positive RT-qPCR result may not necessarily mean the person is still infectious or that they still have any meaningful disease. The RNA could be from non-viable virus and/or the amount of live virus may be too low for transmission.

Cycle threshold (Ct) values

RT-qPCR provides quantification by first reverse transcribing RNA into DNA, and then performing qPCR where a fluorescence signal increases proportionally to the amount of amplified nucleic acid. The test is positive if the fluorescence reaches a specified threshold within a certain number of PCR cycles (Ct value, inversely related to the viral load). Many qPCR assays use a Ct cut-off of 40, allowing detection of very few starting RNA molecules. Some experts (Tom 2020) suggest using this Ct value or to calculate viral load which can help refine decision-making (shorter isolation, etc). Unfortunately, there is still a wide heterogeneity and inconsistency of the standard curves calculated from studies that provide Ct values from serial dilution samples and the estimated viral loads. According to other experts, precautions are needed when interpreting the Ct values of SARS-CoV-2 RT-PCR results shown in COVID-19 publications to avoid misunderstanding of viral load kinetics for comparison across different studies (Han 2020). Caution is needed when regarding Ct values as a surrogate indicator of ‘quantity’ in a qualitative PCR assay (“viral load”). Results are not transferable across different assays, different gene targets and different specimen types (Poon 2020).

However, some clinical key studies are listed here:

- In 678 patients with COVID-19, in-hospital mortality was 35.0% with a “high viral load” (Ct < 25; n = 220), 17.6% with a “medium viral load” (Ct 25-30; n = 216), and 6.2% with a “low viral load” (Ct > 30; n = 242). High viral load was independently associated with mortality (adjusted odds ratio 6.05; 95% CI: 2.92-12.52) and intubation (aOR 2.73; 95% CI: 1.68-4.44) in multivariate models (Magleby 2020).
- A prospective serial sampling of 70 patients revealed clinically relevant Ct values, namely a Ct of 24 (“high viral load”), and > 40 (“negative”), occurred 9 and 36 days after symptom onset (Lesho 2020).
- Among 93 household members (including index cases) who tested positive for SARS-CoV-2 by NP swab, Ct values were lowest soon after symptom onset and were significantly correlated with time elapsed since onset; within

7 days after symptom onset, the median Ct value was 26.5, compared with a median Ct value of 35.0 at 21 days after onset (Salvatore 2020).

- Virus culture was attempted from 324 samples (from 253 cases) that tested positive for SARS-CoV-2 by RT-PCR. Ct values correlated strongly with cultivable virus. Probability of culturing virus declined to 8% in samples with Ct > 35 and to 6% (95% CI: 0.9–31.2%) 10 days after onset (Singanayagam 2020).
- A cross-sectional study determined PCR positive samples for their ability to infect cell lines. Of 90 samples, only 29% demonstrated viral growth. There was no growth in samples with a Ct > 24 or duration of symptoms > 8 days (Bullard 2020).

Test systems other than conventional RT-PCR

Access to rapid diagnosis is key to the control of the SARS-CoV-2 pandemic. In the future, point-of-care testing could relieve pressure on centralized laboratories and increase overall testing capacity. Besides PCR, additional potentially valuable amplification/detection methods, such as CRISPR (targeting clustered regularly interspaced short palindromic repeats), isothermal nucleic acid amplification technologies (e.g. reverse transcription loop-mediated isothermal amplification (RT-LAMP), and molecular microarray assays are under development or are in the process of being commercialized. According to WHO on September 11, validation of the analytic and clinical performance of these assays, demonstration of their potential operational utility, rapid sharing of data, as well as emergency regulatory review of manufacturable, well-performing tests “are encouraged to increase access to SARS-CoV-2 testing” (WHO 20200911).

Point-of-care tests

Point-of-care tests are easy-to-use devices to facilitate testing outside of laboratory settings (Guglielmi 2020, Jouni 2020). They are eagerly awaited. But will they be game-changers? On May 6, the FDA granted an emergency use authorization for a CRISPR-based SARS-CoV-2 fluorescent assay marketed by Sherlock Biosciences. This straightforward SARS-CoV-2 test combines simplified extraction of viral RNA with isothermal amplification and CRISPR-mediated detection. The results are available within an hour with minimal equipment. First results (n = 202 positive/200 negative samples): sensitivity 93.1%, specificity 98.5% (Jouni 2020). However, its use still remains limited to laboratories certified to perform high-complexity tests. There are other reports of an all-in-one dual CRISPR-Cas12a assay (Ding 2020) which allows all components to be incubated in one pot for CRISPR-based nucleic acid detec-

tion, enabling simple, all-in-one molecular diagnostics without the need for separate and complex manual operations.

On May 6, FDA also authorized (EUA) Quidel's Sofia 2 SARS Antigen Fluorescent Immunoassay. This test must be read on a dedicated analyzer and detects SARS-CoV-2 nucleocapsid protein from nasopharyngeal swabs in 15 min. According to the manufacturer, the assay demonstrated acceptable clinical sensitivity and detected 47/59 infections (80%). In another study, the so called CovidNudge test had 94% sensitivity and 100% specificity when compared with standard laboratory-based RT-PCR (Gibani 2020). In other studies, sensitivity was much lower. The BIOCREREDIT COVID-19 antigen test was 10,000 fold less sensitive than RT-PCR and detected between 11.1 % and 45.7% of RT-PCR-positive samples from COVID-19 patients (Mak 2020).

Besides antigen tests, several rapid nucleic acid amplification tests have been recently released (Collier 2020). The Abbott ID NOW COVID-19 assay (using isothermal nucleic acid amplification of the RdRp viral target) is capable of producing positive results in as little as 5 minutes. In one study, results were compared with RT-PCR Cepheid Xpert Xpress SARS-CoV-2 using nasopharyngeal swabs (Basu 2020). Regardless of method of collection and sample type, the rapid test had negative results in a third of the samples that tested positive by PCR when using nasopharyngeal swabs in viral transport media and 45% when using dry nasal swabs. Such "Reverse Transcription Loop-Mediated Isothermal Amplification" tests (RT-LAMP) could be used outside of a central laboratory on various types of biological samples. They can be completed by individuals without specialty training or equipment and may provide a new diagnostic strategy for combating the spread of SARS-CoV-2 at the point-of-risk (Lamb 2020).

Given the low (or still unproven) sensitivity, these tests may mainly serve as an early adjunctive tool to identify infectious individuals very rapidly, i.e. in the emergency unit. These tests help to avoid bed closure, allow discharge to care homes and expedite access to hospital procedures. Some experts are even more optimistic: the frequent use of cheap, simple, rapid tests is essential, even if their analytic sensitivities are vastly inferior to those of benchmark tests. The key question is not how well molecules can be detected in a single sample - but how effectively infections can be detected in a population by the repeated use of a given test as part of an overall testing strategy - the sensitivity of the testing regimen (Mina 2020).

Diagnosis in the setting of a shortage of PCR test kits

There is no doubt that the overall goal must be to detect as many infections as possible. However, in many countries, a shortage of supply test kits does

not meet the needs of a growing infected population. Especially in low-prevalence settings, sample pooling is an option to reduce costs and speed results. In this approach, small volumes of samples from multiple patients are combined into a single test, resulting in substantial reagent savings. Several studies have shown that 5-10 samples can be pooled, without compromising the results (Ben-Ami 2020, Schmidt 2020). However, pooling is not that trivial (Mallapaty 2020). There are several caveats and careful and rigorous investigation is necessary to assure that the pooling of specimens does not impact the analytical sensitivity of the assay (review: Clark 2020).

Some studies have investigated whether the diagnosis in high prevalence periods and countries can be made without PCR detection if necessary. A large retrospective case-control study from Singapore has evaluated predictors for SARS-CoV-2 infection, using exposure risk factors, demographic variables, clinical findings and clinical test results (Sun 2020). Even in the absence of exposure risk factors and/or radiologic evidence of pneumonia, clinical findings and tests can identify subjects at high risk of COVID-19. Low leukocytes, low lymphocytes, higher body temperature, higher respiratory rate, gastrointestinal symptoms and decreased sputum production were strongly associated with a positive SARS-CoV-2 test. However, those preliminary prediction models are sensitive to the local epidemiological context and phase of the global outbreak. They only make sense during times of high incidence. In other words: if I see a patient during the peak of an epidemic presenting with fever, cough, shortness of breath and lymphopenia, I can be almost sure that this patient suffers from COVID-19. During phases when the incidence is lower, these models do not make sense. There is no doubt that the nucleic acid test serves as the gold standard method for confirmation of infection. Whenever PCR is available, PCR should be performed.

Serology (antibody testing)

Detection of past viral infections by looking for antibodies an infected person has produced will be among the most important goals in the fight against the COVID-19 pandemic. Antibody testing is multipurpose: these serological assays are of critical importance to determine seroprevalence, previous exposure and identify highly reactive human donors for the generation of convalescent serum as therapeutic. They will support contact tracing and screening of health care workers to identify those who are already immune. How many people really got infected, in how many did the virus escape the PCR diagnosis, and for what reasons, how many patients are asymptomatic, and what is the real mortality rate in a defined population? Only with comprehensive serology testing (and well-planned epidemiological studies) will we be able to

answer these questions and reduce the ubiquitous undisclosed number in the current calculations. Several investigations are already underway in a wide variety of locations worldwide.

In recent weeks it has become clear that serology testing may also aid as a complementary diagnostic tool for COVID-19. The seroconversion of specific IgM and IgG antibodies were observed as early as the 4th day after symptom onset. Antibodies can be detected in the middle and later stages of the illness (Guo L 2020, Xiao DAT 2020). If a person with a highly suspicious COVID-19 remains negative by PCR testing and if symptoms are ongoing for at least several days, antibodies may be helpful and enhance diagnostic sensitivity.

However, antibody testing is not trivial. The molecular heterogeneity of SARS-CoV-2 subtypes, imperfect performance of available tests and cross-reactivity with seasonal CoVs have to be considered (reviews: Cheng 2020, Krammer 2020). According to a Cochrane analysis on 57 publications with 15,976 samples, the sensitivity of antibody tests is too low in the first week from symptom onset to have a primary role in the diagnosis of COVID-19. However, these tests may still have a role in complementing other testing in individuals presenting later, when RT-PCR tests are negative or are not done (Deeks 2020). Antibody tests are likely to have a useful role in detecting previous SARS-CoV-2 infection if used 15 or more days after the onset of symptoms. Data beyond 35 days post-symptom onset is scarce. According to the authors, studies of the accuracy of COVID-19 tests require considerable improvement. Studies must report data on sensitivity disaggregated by time from onset of symptoms. A practical overview of the pitfalls of antibody testing and how to communicate risk and uncertainty is given by Watson 2020.

Tests

Average sensitivity and specificity of FDA-approved antibody tests is 84.9% and 98.6%, respectively. Given variable prevalence of COVID-19 (1%-15%) in different parts, statistically the positive predictive value will be as low as 30% to 50% in areas with low prevalence (Mathur 2020). A systematic review of 40 studies on sensitivity and specificity was recently published (Lisboa-Bastos 2020), stratified by method of serological testing (enzyme linked immunosorbent assays - ELISAs), lateral flow immunoassays (LFIAs), or chemiluminescent immunoassays - CLIAs). The pooled sensitivity of ELISAs measuring IgG or IgM was 84.3% (95% confidence interval 75.6% to 90.9%), of LFIAs was 66.0% (49.3% to 79.3%), and of CLIAs was 97.8% (46.2% to 100%). According to the authors, higher quality clinical studies assessing the diagnostic accuracy of serological tests for COVID-19 are urgently needed.

A nice overview of the different platforms, including binding assays such as enzyme-linked immunosorbent assays (ELISAs), lateral flow assays, or Western blot-based assays is given by Krammer 2020. In addition, functional assays that test for virus neutralization, enzyme inhibition, or bactericidal assays can also inform on antibody-mediated immune responses. Many caveats and open questions with regard to antibody testing are also discussed.

Antibody testing usually focuses on antigens (proteins). In the case of SARS-CoV-2, different ELISA kits based on recombinant nucleocapsid protein and spike protein are used (Loeffelholz 2020). The SARS-CoV-2 spike protein seems to be the best target. However, which part of the spike protein to use is less obvious and there is a lot hanging on the uniqueness of the spike protein. The more unique it is, the lower the odds of cross-reactivity with other coronaviruses—false positives resulting from immunity to other coronaviruses. Cross reactivity to other coronaviruses can be challenging. So called confirmation tests (usually neutralization tests) can be used to reduce false positive testings. However, detection and quantification of neutralizing antibodies are relatively low-throughput and limited to Biosafety Level 3-equipped research laboratories. To avoid neutralization tests that require live pathogen and a biosafety level 3 laboratory, several studies have proposed tests based on antibody-mediated blockage of the interaction between the ACE2 receptor protein and the receptor-binding domain. The tests achieved 99.93% specificity and 95–100% sensitivity (Tan 2020).

Even with a very high specificity of 99% and above, however, especially in low-prevalence areas, the informative value of antibody testing is limited and a high rate of false positive tests can be assumed. An example: With a specificity of 99%, it is expected that one test out of 100 is positive. In a high prevalence setting, this is less relevant. However, if a person is tested in a low prevalence setting, the likelihood that a positive test is really positive (the positive predictive value, i.e. the number of really positive tests divided by the number of all positive tests) is low. In a population with a given prevalence of 1%, the predictive value would only be 50%! Current estimates from Iceland, a well-defined but unselected population, still have shown a relatively constant rate of around 0.8% in March 2020 (Gudbjartsson 2020). Even in apparently more severely affected countries, the infection rates are only slightly higher. General antibody screening in these populations will therefore produce a fairly high rate of false positive tests. When assessing anti-SARS-CoV-2 immune status in individuals with low pre-test probability, it may be better to confirm positive results from single measurements by alternative serology tests or functional assays (Behrens 2020).

Some key studies with head-to-head-assessments of different immunoassays

- Abbott, EUROIMMUN and the Elecsys (Roche): The Abbott assay demonstrated the fewest false negative results > 14d post-symptom onset and the fewest false positive results. While the Roche assay detected more positive results earlier after onset of symptoms, none of the assays demonstrated high enough clinical sensitivity before day 14 from symptom onset to diagnose acute infection (Tang 2020).
- Abbott, LIAISON (DiaSorin), Elecsys (Roche), Siemens, plus a novel in-house 384-well (Oxford) ELISA in 976 (!) pre-pandemic blood samples and 536 (!) blood samples with confirmed SARS-CoV-2 infection. All assays had a high sensitivity (92.7-99.1%) and specificity (98.7-99.9%). The most sensitive test assessed was the in-house ELISA. The Siemens assay and Oxford immunoassay achieved 98% sensitivity/specificity without further optimization. However, a limitation was the small number of pauci-symptomatic and asymptomatic cases analyzed (NAEG 2020).
- Abbott, Epitope Diagnostics, EUROIMMUN, and Ortho Clinical Diagnostics: all four immunoassays performed similarly with respect to sensitivity in COVID-19 hospitalized patients, and except for the Epitope assay, also in individuals with milder forms of the infection (Theel 2020). The Abbott and Ortho Clinical immunoassays provided the highest overall specificity, of over 99%.

Indication in clinical practice

But outside clinical studies, who should be tested now? Testing actually makes no sense for patients with a previous, proven COVID-19 disease. However, it can still be done if, for example, you want to validate a test. In addition to those involved in health care or working in other professions with a high risk of transmission, such testing can also be useful in order to identify possible contact persons retrospectively. However, we only measure antibodies when the testing result might have consequences. Patients should be informed about the low positive predictive value, especially in those without any evidence of prior disease or exposition to COVID-19. In these patients, antibody testing is not recommended. Outside epidemiological hot spots, in low prevalence countries like Germany, virtually everybody is still seronegative. If positive, the predictive value is too low.

The kinetics of antibodies

Serologic responses to coronaviruses are only transient. A brilliant systematic review of antibody-mediated immunity to coronaviruses (kinetics, correlates

of protection, and association with severity) was recently published ([Huang AT 2020](#)).

Antibodies to other human, seasonal coronaviruses may disappear even after a few months. Preliminary data suggest that the profile of antibodies to SARS-CoV-2 is similar to SARS-CoV ([Xiao DAT 2020](#)). For SARS-CoV, antibodies were not detected within the first 7 days of illness, but IgG titre increased dramatically on day 15, reaching a peak on day 60, and remained high until day 180 from when it declined gradually until day 720. IgM was detected on day 15 and rapidly reached a peak, then declined gradually until it was undetectable on day 180 ([Mo 2006](#)). As with other viruses, IgM antibodies occur somewhat earlier than IgG antibodies which are more specific. IgA antibodies are relatively sensitive but less specific ([Okba 2020](#)).

The first larger study on the host humoral response against SARS-CoV-2 has shown that these tests can aid the diagnosis of COVID-19, including subclinical cases ([Guo 2020](#)). In this study, IgA, IgM and IgG response using an ELISA-based assay on the recombinant viral nucleocapsid protein was analyzed in 208 plasma samples from 82 confirmed and 58 probable cases ([Guo 2020](#)). The median duration of IgM and IgA antibody detection were 5 days (IQR 3-6), while IgG was detected on day 14 (IQR 10-18) after symptom onset, with a positive rate of 85%, 93% and 78% respectively. The detection efficiency by IgM ELISA was higher than that of PCR after 5.5 days of onset of symptoms. In another study of 173 patients, the seroconversion rates (median time) for IgM and IgG were 83% (12 days) and 65% (14 days), respectively. A higher titer of antibodies was independently associated with severe disease ([Zhao 2020](#)). In other studies, however, antibody level did not correlate clearly with clinical outcomes ([Ren 2020](#)).

In some patients, IgG occurs even faster than IgM. In a study on seroconversion patterns of IgM and IgG antibodies, the seroconversion time of IgG antibody was earlier than IgM. IgG antibody reached the highest concentration on day 30, while IgM antibody peaked on day 18, but then began to decline ([Qu J 2020](#)). The largest study to date reported on acute antibody responses in 285 patients (mostly non-severe COVID-19). Within 19 days after symptom onset, 100% of patients tested positive for antiviral IgG. Seroconversion for IgG and IgM occurred simultaneously or sequentially. Both IgG and IgM titers plateaued within 6 days after seroconversion. The median day of seroconversion for both IgG and IgM was 13 days post-symptom onset. No association between plateau IgG levels and clinical characteristics was found ([Long 2020](#)).

However, there is some evidence that asymptomatic individuals develop less strong antibody responses. Moreover, antibodies disappear from the blood. Your COVID pass expires within a few weeks. Compared to symptomatic pa-

tients, 37 asymptomatic patients had lower virus-specific IgG levels in the acute phase (Long Q 2020). IgG levels and neutralizing antibodies started to decrease within 2–3 months after infection. Of note, 40% became seronegative (13% of the symptomatic group) for IgG in the early convalescent phase. Among 19 health care workers who had anti-SARS-CoV-2 antibodies detected at baseline, only 8 (42%) had antibodies that persisted above the seropositivity threshold at 60 days, whereas 11 (58%) became seronegative (Patel 2020). A decrease in anti-RBD antibody level was also seen in 15 donors of convalescent plasma (Perreault 2020).

Taken together, antibody testing is not only an epidemiological tool. It may also help in diagnosis. It will be seen in the coming months how the human antibody response to SARS-CoV-2 evolves over time and how this response and titres correlate with immunity. It is also conceivable that in some patients (e.g. those with immunodeficiency) the antibody response remains reduced.

Radiology

Chest computed tomography

Computed tomography (CT) can play a role in both diagnosis and assessment of disease extent and follow-up. Chest CT has a relatively high sensitivity for diagnosis of COVID-19 (Ai 2020, Fang 2020). However, around half of patients may have a normal CT during the first 1–2 days after symptom onset (Bernheim 2020). On the other hand, it became clear very early in the current pandemic that a considerable proportion of subclinical patients (scans done before symptom onset) may already have pathological CT findings (Chan 2020, Shi 2020). In some of these patients showing pathological CT findings evident for pneumonia, PCR in nasopharyngeal swabs was still negative (Xu 2020). On the other hand, half of the patients who later develop CT morphologically visible pneumonia can still have a normal CT in the first 1–2 days after the symptoms appear (Bernheim 2020).

However, one should not overestimate the value of chest CT. The recommendation by some Chinese researchers to include CT as an integral part in the diagnosis of COVID-19 has led to harsh criticism, especially from experts in Western countries. The Chinese studies have shown significant errors and shortcomings. In view of the high effort and also due to the risk of infection for the staff, many experts strictly reject the general CT screening in SARS-CoV-2 infected patients or in those suspected cases (Hope 2020, Raptis 2020). According to the recommendation of the British Radiology Society, which made attempts to incorporate CT into diagnostic algorithms for COVID-19

diagnostics, the value of CT remains unclear – even if a PCR is negative or not available (Nair 2020, Rodrigues 2020). A chest CT should only be performed if complications or differential diagnoses are considered (Raptis 2020).

In blinded studies, radiologists from China and the United States have attempted to differentiate COVID-19 pneumonia from other viral pneumonia. The specificity was quite high, the sensitivity much lower (Bai 2020). A recent metaanalysis found a high sensitivity but low specificity (Kim 2020). The sensitivity of CT was affected by the distribution of disease severity, the proportion of patients with comorbidities, and the proportion of asymptomatic patients. In areas with low prevalence, chest CT had a low positive predictive value (1.5-30.7%).

If pathological, images usually show bilateral involvement, with multiple patchy or ground-glass opacities (GGO) with subpleural distribution in multiple bilateral lobes. Lesions may display significant overlap with those of SARS and MERS (Hosseiny 2020). According to a review of 45 studies comprising 4410 (!) patients, ground glass opacities (GGOs), whether isolated (50%) or co-existing with consolidations (44%) in bilateral and subpleural distribution, were the most prevalent chest CT findings (Ojha 4410). Another systematic review of imaging findings in 919 patients found bilateral multilobar GGO with a peripheral or posterior distribution, mainly in the lower lobes and less frequently within the right middle lobe as the most common feature (Salehi 2020). In this review, atypical initial imaging presentation of consolidative opacities superimposed on GGO were found in a smaller number of cases, mainly in the elderly population. Septal thickening, bronchiectasis, pleural thickening, and subpleural involvement were less common, mainly in the later stages of the disease. Pleural effusion, pericardial effusion, lymphadenopathy, cavitation, CT halo sign, and pneumothorax were uncommon (Salehi 2020).

The evolution of the disease on CT is not well understood. However, with a longer time after the onset of symptoms, CT findings are more frequent, including consolidation, bilateral and peripheral disease, greater total lung involvement, linear opacities, “crazy-paving” pattern and the “reverse halo” sign (Bernheim 2020). Some experts have proposed that imaging can be sorted into four different phases (Li M 2020). In the early phase, multiple small patchy shadows and interstitial changes emerge. In the progressive phase, the lesions increase and enlarge, developing into multiple GGOs as well as infiltrating consolidation in both lungs. In the severe phase, massive pulmonary consolidations and “white lungs” are seen, but pleural effusion is rare. In the dissipative phase, the GGOs and pulmonary consolidations were completely absorbed, and the lesions began to change into fibrosis.

In a longitudinal study analyzing 366 serial CT scans in 90 patients with COVID-19 pneumonia, the extent of lung abnormalities progressed rapidly and peaked during illness days 6-11 (Wang Y 2020). The predominant pattern of abnormalities after symptom onset in this study was ground-glass opacity (45-62%). As pneumonia progresses, areas of lesions enlarge and developed into diffuse consolidations in both lungs within a few days (Guan 2020).

Most patients discharged had residual disease on final CT scans (Wang Y 2020). Studies with longer follow-up are needed to evaluate long-term or permanent lung damage including fibrosis, as is seen with SARS and MERS infections. Pulmonary fibrosis is expected to be the main factor leading to pulmonary dysfunction and decline of quality of life in COVID-19 survivors after recovery. More research is needed into the correlation of CT findings with clinical severity and progression, the predictive value of baseline CT or temporal changes for disease outcome, and the sequelae of acute lung injury induced by COVID-19 (Lee 2020).

Of note, chest CT is not recommended in all COVID-19 patients, especially in those who are well enough to be sent home or those with only short symptomatic times (< 2 days). In the case of COVID-19, a large number of patients with infection or suspected infection swarm into the hospital. Consequently, the examination workload of the radiology department increases sharply. Because the transmission route of SARS-CoV-2 is through respiratory droplets and close contact transmission, unnecessary CT scan should be avoided. An overview of the prevention and control of the COVID-19 epidemic in the radiology department is given by An et al.

Ultrasound, PET and other techniques

Some experts have postulated that lung ultrasound (LUS) may be helpful, since it can allow the concomitant execution of clinical examination and lung imaging at the bedside by the same doctor (Buonsenso 2020, Soldati 2020). Potential advantages of LUS include portability, bedside evaluation, safety and possibility of repeating the examination during follow-up. Experience especially from Italy with lung ultrasound as a bedside tool has improved evaluation of lung involvement, and may also reduce the use of chest x-rays and CT. A point scoring system is employed by region and ultrasound pattern (Vetrugno 2020). However, the diagnostic and prognostic role of LUS in COVID-19 is uncertain.

Whether there is any potential clinical utility of other imaging techniques such as 18F-FDG PET/CT imaging in the differential diagnosis of complex cases also remains unclear (Deng 2020, Qin 2020).

In patients with neurological symptoms, brain MRI is often performed. In 27 patients, the most common imaging finding was cortical signal abnormalities on FLAIR images (37%), accompanied by cortical diffusion restriction or leptomeningeal enhancement (Kandemirli 2020). However, the complex clinical course including comorbidities, long ICU stay with multidrug regimens, respiratory distress with hypoxia episodes can all act as confounding factors and a clear cause-effect relationship between COVID-19 infection and MRI findings will be hard to establish.

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7. Clinical Presentation

Christian Hoffmann

Bernd Sebastian Kamps

After an average incubation time of around 5 days (range: 2-14 days), a typical COVID-19 infection begins with dry cough and low-grade fever (38.1–39°C or 100.5–102.1°F), often accompanied by diminishment of smell and taste. In most patients, COVID-19 remains mild or moderate and symptoms resolve within a week and patients typically recover at home. Around 10% of patients remain symptomatic through the second week. The longer the symptoms persist, the higher the risk of developing more severe COVID-19, requiring hospitalization, intensive care and invasive ventilation. The outcome of COVID-19 is often unpredictable, especially in older patients with comorbidities. The clinical picture ranges from completely asymptomatic to rapidly devastating courses.

In this chapter we discuss the clinical presentation, including

- The incubation period
- Asymptomatic patients
- Frequent and rare symptoms
- Laboratory findings
- Outcome: Risk factors for severe disease
- Reactivations and reinfections
- Long-term sequelae

The radiological findings are described in the diagnostic chapter, page 249.

Incubation period

A pooled analysis of 181 confirmed COVID-19 cases with identifiable exposure and symptom onset windows estimated the median incubation period to be 5.1 days with a 95% CI of 4.5 to 5.8 days (Lauer 2020). The authors estimated that 97.5% of those who develop symptoms will do so within 11.5 days (8.2 to 15.6 days) of infection. Fewer than 2.5% of infected persons will show symptoms within 2.2 days, whereas symptom onset will occur within 11.5 days in 97.5%. However, these estimates imply that, under conservative assumptions, 101 out of every 10,000 cases will develop symptoms after 14 days of active monitoring or quarantine. Another analysis of 158 confirmed cases outside Wuhan estimated a similar median incubation period of 5.0 days (95 % CI, 4.4

to 5.6 days), with a range of 2 to 14 days (Linton 2020). In a detailed analysis of 36 cases linked to the first three clusters of circumscribed local transmission in Singapore, the median incubation period was 4 days with a range of 1-11 days (Pung 2020). Taken together, the incubation period of around 4-6 days is in line with that of other coronaviruses causing SARS or MERS (Virlogeux 2016). Of note, the time from exposure to onset of infectiousness (latent period) may be shorter. There is little doubt that transmission of SARS-CoV-2 during the late incubation period is possible (Li 2020). In a longitudinal study, the viral load was high 2-3 days before the onset of symptoms, and the peak was even reached 0.7 days before the onset of symptoms. The authors of this *Nature Medicine* paper estimated that approximately 44% (95% CI 25-69%) of all secondary infections are caused by such presymptomatic patients (He 2020).

Asymptomatic cases

Understanding the frequency of asymptomatic patients and the temporal course of asymptomatic transmission will be crucial for assessing disease dynamics. It is important to distinguish those patients who will remain asymptomatic during the whole time of infection and those in which infection is still too early to cause symptoms (presymptomatic). While physicians need to be aware of asymptomatic cases, the true percentage is difficult to assess. To evaluate symptoms systematically is not trivial and the ascertainment process could lead to misclassification. If you do not ask precisely enough, you will get false negative answers. If questions are too specific, the interviewees may give false positive answers (confirmation bias). For example, in a large study, only two thirds of patients reporting olfactory symptoms had abnormal results in objective olfactory testing (see below). What is a symptom? And, is it possible to interview the demented residents of a nursing home? Sweet grandma will say she was fine over the last few weeks.

In a living systematic review (through June 10, 2020, analyzing 79 studies in a range of different settings), 20% (95% CI 17%-25%) remained asymptomatic during follow-up, but biases in study designs limit the certainty of this estimate (Buitrago-Garcia 2020). In seven studies of defined populations screened for SARS-CoV-2 and then followed, 31% (95% CI 26%-37%) remained asymptomatic. Another review found that asymptomatic persons seem to account for approximately 40-45% of infections, and that they can transmit the virus to others for an extended period, perhaps longer than 14 days. The absence of COVID-19 symptoms might not necessarily imply an absence of harm as sub-clinical lung abnormalities are frequent (Oran 2020).

The probable best data come from 3,600 people on board the cruise ship Diamond Princess (Mizumoto 2020) who became involuntary actors in a “well-

controlled experiment” where passengers and crew comprised an environmentally homogeneous cohort. Due to insufficient hygienic conditions, > 700 people became infected while the ship was quarantined in the port of Yokohama, Japan. After systematic testing, 328 (51.7%) of the first 634 confirmed cases were found to be asymptomatic. Considering incubation periods between 5.5 and 9.5 days, the authors calculated the true asymptomatic proportion at 17.9% (Mizumoto 2020). The outbreak at the aircraft carrier USS Theodore Roosevelt revealed that 146/736 infected sailors (19.8%) remained asymptomatic for the duration of the study period.

Table 1. Larger studies with defined populations; proportion of asymptomatic patients (LTF = long-term facilities)

	Population, n	Asymptomatic
Alvarado 2020	Young sailors, US Aircraft Carrier (n=736)	20%
Borras-Bermejo 2020	Nursing Homes Spain, residents (n=768) and staff (n=403)	68% of residents, 56% of staff (including pre-symptomatic)
Feaster 2020	LTFs California, residents and staff (n=631)	19-86% of residents, 17-31% of staff
Gudbjartsson 2020	Icelandic Population (n=1,221)	43% (including pre-symptomatic)
Hoxha 2020	LTFs Belgium, residents (n=4,059) and staff (n=2,185)	75% of residents, 74% of staff (including pre-symptomatic)
Lavezzo 2020	(Small town) Vo, Italy, all residents (n=2,812)	43%
Marossy 2020	LTFs London (n=2,455)	51% of residents, 69% of staff

There is no doubt that asymptomatic patients may transmit the virus (Bai 2020, Rothe 2020). In several studies from Northern Italy or Korea, viral loads in nasal swabs did not differ significantly between asymptomatic and symptomatic subjects, suggesting the same potential for transmitting the virus (Lee 2020). Of 63 asymptomatic patients in Chongqing, 9 (14%) transmitted the virus to others (Wang Y 2020).

Taken together, these preliminary studies indicate that a significant proportion (20-60%) of all COVID-19 infected subjects may remain asymptomatic during their infection. The studies show a broad range, depending on the populations and probably on methodological issues. It will be very difficult (if not impossible) to clarify the exact proportion.

Symptoms

A plethora of symptoms have been described in the past months, clearly indicating that COVID-19 is a complex disease, which in no way consists only of a respiratory infection. Many symptoms are unspecific so that the differential diagnosis encompasses a wide range of infections, respiratory and other diseases. However, different clusters can be distinguished in COVID-19. The most common symptom cluster encompasses the respiratory system: cough, sputum, shortness of breath, and fever. Other clusters encompass musculoskeletal symptoms (myalgia, joint pain, headache, and fatigue), enteric symptoms (abdominal pain, vomiting, and diarrhea); and less commonly, a mucocutaneous cluster. An excellent review on these extrapulmonary organ-specific pathophysiology, presentations and management considerations for patients with COVID-19 was recently published ([Gupta 2020](#)).

Fever, cough, shortness of breath

Symptoms occur in the majority of cases (for asymptomatic patients, see below). In early studies from China ([Guan 2020](#), [Zhou 2020](#)), fever was the most common symptom, with a median maximum of 38.3 C; only a few had a temperature of > 39 C. The absence of fever seems to be somewhat more frequent than in SARS or MERS; fever alone may therefore not be sufficient to detect cases in public surveillance. The second most common symptom was cough, occurring in about two thirds of all patients. Among survivors of severe COVID-19 ([Zhou 2020](#)), median duration of fever was 12.0 days (8-13 days) and cough persisted for 19 days (IQR 12-23 days). According to a systemic review, including 148 articles comprising 24,410 adults with confirmed COVID-19 from 9 countries ([Grant 2020](#)), the most prevalent symptoms were fever (78%), cough (57%) and fatigue (31%).

Fever and cough do not distinguish between mild and severe cases nor do they predict the course of COVID-19 ([Richardson 2020](#), [Petrilli 2020](#)). In contrast, shortness of breath has been identified as a strong predictor of severe disease in larger studies. In a cohort of 1,590 patients, dyspnea was associated with an almost two-fold risk for critical disease ([Liang 2020](#)) and mortality ([Chen 2020](#)). Others found higher rates of shortness of breath, and temperature of > 39.0 in older patients compared with younger patients ([Lian 2020](#)). In the Wuhan study on patients with severe COVID-19, a multivariate analysis revealed that a respiratory rate of > 24 breaths per minute at admission was higher in non-survivors (63% versus 16%).

Over the last weeks, much cohort data from countries outside China have been published. However, almost all data applies to patients who were admit-

ted to hospitals, indicating selection bias towards more severe and symptomatic patients.

- Among 20,133 patients in the UK who were admitted to 208 acute care hospitals in the UK between 6 February and 19 April 2020, the most common symptoms were cough (69%), fever (72%), and shortness of breath (71%), showing a high degree of overlap ([Docherty 2020](#)).
- Among 5,700 patients who were admitted to any of 12 acute care hospitals in New York between March 1, 2020, and April 4, 2020, only 30.7% had fever of > 38C. A respiratory rate of > 24 breaths per minute at admission was found in 17.3% ([Richardson 2020](#)).
- Among the first 1,000 patients presenting at the NewYork Presbyterian/Columbia University ([Argenziano 2020](#)), the most common presenting symptoms were cough (73%), fever (73%), and dyspnea (63%).

Musculoskeletal symptoms

The cluster of musculoskeletal symptoms encompasses myalgia, joint pain, headache, and fatigue. These are frequent symptoms, occurring each in 15-40% of patients ([Argenziano 2020](#), [Docherty 2020](#), [Guan 2020](#)). Although subjectively very disturbing and sometimes foremost in the perception of the patient, these symptoms tell us nothing about the severity of the clinical picture. However, they are frequently overlooked in clinical practice, and headache merits special attention.

According to a recent review ([Bolay 2020](#)), headache is observed in 11-34% of hospitalized COVID-19 patients, occurring in 6-10% as the presenting symptom. Significant features are moderate-severe, bilateral headache with pulsating or pressing quality in the temporo-parietal, forehead or periorbital region. The most striking features are sudden to gradual onset and poor response to common analgesics. Possible pathophysiological mechanisms include activation of peripheral trigeminal nerve endings by the SARS-CoV-2 directly or through the vasculopathy and/or increased circulating pro-inflammatory cytokines and hypoxia.

Gastrointestinal symptoms

Cell experiments have shown that SARS-CoV and SARS-CoV-2 are able to infect enterocytes ([Lamers 2020](#)). Active replication has been shown in both bats and human intestinal organoids ([Zhou 2020](#)). Fecal calprotectin as a reliable fecal biomarker allowing detection of intestinal inflammation in inflammatory bowel diseases and infectious colitis, was found in some patients, providing evidence that SARS-CoV-2 infection instigates an inflammatory

response in the gut ([Effenberger 2020](#)). These findings explain why gastrointestinal symptoms are observed in a subset of patients and why viral RNA can be found in rectal swabs, even after nasopharyngeal testing has turned negative. In patients with diarrhea, viral RNA was detected at higher frequency in stool ([Cheung 2020](#)).

In the early Chinese studies, however, gastrointestinal symptoms were rarely seen. In a meta-analysis of 60 early studies comprising 4,243 patients, the pooled prevalence of gastrointestinal symptoms was 18% (95% CI, 12%-25%); prevalence was lower in studies in China than other countries. As with otolaryngeal symptoms, it remains unclear whether this difference reflects geographic variation or differential reporting. Among the first 393 consecutive patients who were admitted to two hospitals in New York City, diarrhea (24%), and nausea and vomiting (19%) were relatively frequent ([Goyal 2020](#)). Among 18,605 patients admitted to UK Hospitals, 29% of all patients complained of enteric symptoms on admission, mostly in association with respiratory symptoms; however, 4% of all patients described enteric symptoms alone ([Docherty 2020](#)).

It's not all critical illness. Another study compared 92 critically ill patients with COVID-19-induced ARDS with 92 comparably ill patients with non-COVID-19 ARDS, using propensity score analysis. Patients with COVID-19 were more likely to develop gastrointestinal complications (74% vs 37%; $p < 0.001$). Specifically, patients with COVID-19 developed more transaminitis (55% vs 27%), severe ileus (48% vs 22%), and bowel ischemia (4% vs 0%). High expression of ACE 2 receptors along the epithelial lining of the gut that act as host-cell receptors for SARS-CoV-2 could explain this ([El Moheb 2020](#)).

Otolaryngeal symptoms (including anosmia)

Although upper respiratory tract symptoms such as rhinorrhea, nasal congestion, sneezing and sore throat are relatively unusual, it has become clear within a few weeks that anosmia and hyposmia are important signs of the disease ([Luers 2020](#)). Interestingly, these otolaryngological symptoms appear to be much more common in Europe than in Asia. However, it is still unclear whether this is a real difference or whether these complaints were not recorded well enough in the initial phase in China. There is now very good data from Europe: the largest study to date found that 1,754/2,013 patients (87%) reported loss of smell, whereas 1,136 (56%) reported taste dysfunction. Most patients had loss of smell after other general and otolaryngologic symptoms ([Lechien 2020](#)). Mean duration of olfactory dysfunction was 8.4 days. Females seem to be more affected than males. The prevalence of self-reported smell and taste dysfunction was higher than previously reported and may be char-

acterized by different clinical forms. Anosmia may not be related to nasal obstruction or inflammation. Of note, only two thirds of patients reporting olfactory symptoms and who had objective olfactory testing had abnormal results.

“Flu plus ‘loss of smell’ means COVID-19”. Among 263 patients presenting in March (at a single center in San Diego) with flu-like symptoms, loss of smell was found in 68% of COVID-19 patients (n=59), compared to only 16% in negative patients (n=203). Smell and taste impairment were independently and strongly associated with SARS-CoV-2 positivity (anosmia: adjusted odds ratio 11, 95% CI: 5-24). Conversely, sore throat was independently associated with negativity (Yan 2020).

Among a total of 18,401 participants from the US and UK who reported potential symptoms on a smartphone app and who had undergone a SARS-CoV-2 test, the proportion of participants who reported loss of smell and taste was higher in those with a positive test result (65 vs 22%). A combination of symptoms, including anosmia, fatigue, persistent cough and loss of appetite was appropriate to identify individuals with COVID-19 (Menni 2020).

Post-mortem histological analysis of the olfactory epithelium in two COVID-19 patients showed prominent leukocytic infiltrates in the lamina propria and focal atrophy of the mucosa. However, it is unclear whether the observed inflammatory neuropathy is a result of direct viral damage or is mediated by damage to supporting non-neural cells (Kirschenbaum 2020). Among 49 confirmed COVID-19 patients with anosmia, there were no significant pathological changes in the paranasal sinuses on CT scans. Olfactory cleft and ethmoid sinuses appeared normal while in other sinuses, partial opacification was detected only in some cases (Naeini 2020).

Cardiovascular symptoms and issues

There is growing evidence of direct and indirect effects of SARS-CoV-2 on the heart, especially in patients with pre-existing heart diseases (Bonow 2020). SARS-CoV-2 has the potential to infect cardiomyocytes, pericytes and fibroblasts via the ACE2 pathway leading to direct myocardial injury, but the pathophysiological sequence remains unproven (Hendren 2020). Post-mortem examination by *in situ* hybridization suggested that the most likely localization of SARS-CoV-2 is not in the cardiomyocytes but in interstitial cells or macrophages invading the myocardial tissue (Lindner 2020). A second hypothesis to explain COVID-19-related myocardial injury centers on cytokine excess and/or antibody-mediated mechanisms. It has also been shown that the ACE2 receptor is widely expressed on endothelial cells and that direct

SARS-CoV-2 infection of the endothelial cell is possible, leading to diffuse endothelial inflammation (Varga 2020). Post-mortem examination cases indicate a strong virus-induced vascular dysfunction (Menter 2020).

Clinically, COVID-19 can manifest with an acute cardiovascular syndrome (termed “ACovCS”, for **a**cute **C**COVID-19 **c**ardiovascular syndrome). Numerous cases with ACovCS have been described, not only with typical thoracic complaints, but also with very diverse cardiovascular manifestations. Troponin is an important parameter (see below). In a case series of 18 COVID-19 patients who had ST segment elevation, there was variability in presentation, a high prevalence of non-obstructive disease, and a poor prognosis. 6/9 patients undergoing coronary angiography had obstructive disease. Of note, all 18 patients had elevated D-dimer levels (Bangalore 2020). Among 2,736 COVID-19 patients admitted to one of five hospitals in New York City who had troponin-I measured within 24 hours of admission, 985 (36%) patients had elevated troponin concentrations. After adjusting for disease severity and relevant clinical factors, even small amounts of myocardial injury (0.03-0.09 ng/mL) were significantly associated with death (Lala 2020).

In patients with a seemingly typical coronary heart syndrome, COVID-19 should also be considered in the differential diagnosis, even in the absence of fever or cough (Fried 2020, Inciardi 2020). For more information, see the chapter *Comorbidities*, page 381.

Beside ACovCS, a wide array of cardiovascular manifestations is possible, including heart failure, cardiogenic shock, arrhythmia, and myocarditis. Among 100 consecutive patients diagnosed with COVID-19 infection undergoing complete echocardiographic evaluation within 24 hours of admission, only 32% had a normal echocardiogram at baseline. The most common cardiac pathology was right ventricular (RV) dilatation and dysfunction (observed in 39% of patients), followed by left ventricular (LV) diastolic dysfunction (16%) and LV systolic dysfunction (10%). In another case series of 54 patients with mild-to-moderate COVID-19 in Japan, relative bradycardia was also a common finding (Ikeuchi 2020).

Thrombosis, embolism

Coagulation abnormalities occur frequently in association with COVID-19, complicating clinical management. Numerous studies have reported on an incredibly high number of venous thromboembolism (VTE), especially in those with severe COVID-19. The initial coagulopathy of COVID-19 presents with prominent elevation of D-dimer and fibrin/fibrinogen degradation products, while abnormalities in prothrombin time, partial thromboplastin

time, and platelet counts are relatively uncommon (excellent review: [Connors 2020](#)). Coagulation test screening, including the measurement of D-dimer and fibrinogen levels, is suggested.

But what are the mechanisms? Some studies have found pulmonary embolism with or without deep venous thrombosis, as well as presence of recent thrombi in prostatic venous plexus, in patients with no history of VTE, suggesting *de novo* coagulopathy in these patients with COVID-19. Others have highlighted changes consistent with thrombosis occurring within the pulmonary arterial circulation, in the absence of apparent embolism (nice review: [Deshpande 2020](#)). Some studies have indicated severe hypercoagulability rather than consumptive coagulopathy ([Spiezia 2020](#)) or an imbalance between coagulation and inflammation, resulting in a hypercoagulable state (review: [Colling 2020](#)).

According to a systematic review of 23 studies, among 7,178 COVID-19 patients admitted to general wards and intensive care units (ICU), the pooled in-hospital incidence of pulmonary embolism (PE) or lung thrombosis was 14.7% and 23.4%, respectively ([Roncon 2020](#)).

Some of the key studies are listed here:

- In a single-center study from Amsterdam on 198 hospitalized cases, the cumulative incidences of VTE at 7 and 21 days were 16% and 42%. In 74 ICU patients, cumulative incidence was 59% at 21 days, despite thrombosis prophylaxis. The authors recommend performing screening compression ultrasound in the ICU every 5 days ([Middeldorp 2020](#)).
- Among 3334 consecutive patients admitted to 4 hospitals in New York City, a thrombotic event occurred in 16% ([Bilaloglu 2020](#)). Of these, 207 (6.2%) were venous (3.2% PE and 3.9% DVT) and 365 (11.1%) were arterial (1.6% ischemic stroke, 8.9% MI, and 1.0% systemic thromboembolism). All-cause mortality was 24.5% and was higher in those with thrombotic events (43% vs 21%). D-dimer level at presentation was independently associated with thrombotic events.
- In a retrospective multicentre study, 103/1240 (8.3%) consecutive patients hospitalized for COVID-19 (patients directly admitted to an ICU were excluded) had evidence for PE. In a multivariate analysis, male gender, anticoagulation, elevated CRP, and time from symptom onset to hospitalization were associated with PE risk ([Fauvel 2020](#)).
- Autopsy findings from 12 patients, showing that 7/12 had deep vein thrombosis. Pulmonary embolism was the direct cause of death in four cases ([Wichmann 2020](#)).

- Acute pulmonary embolism (APE) can occur in mild-to moderate and is not limited to severe or critical COVID-19 ([Gervaise 2020](#)).
- Careful examination of the lungs from deceased COVID-19 patients with lungs from 7 patients who died from ARDS secondary to influenza A showed distinctive vascular features. COVID-19 lungs displayed severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes. Histologic analysis of pulmonary vessels showed widespread thrombosis with microangiopathy. Alveolar capillary microthrombi and the amount of vessel growth were 9 and almost 3 times as prevalent as in influenza, respectively ([Ackermann 2020](#)).
- Five cases of large-vessel stroke occurring in younger patients (age 33-49, 2 without any risk factors) ([Oxley 2020](#)).
- Five cases with profound hemodynamic instability due to the development of acute cor pulmonale, among them 4 younger than 65 years of age ([Creel-Bulos 2020](#)).

Empiric therapeutic anti-coagulation (AC) is now being employed in clinical practice in many centers and will be evaluated in randomized clinical trials. To adjust for bias due to non-random allocation of potential covariates among COVID-19 patients, one study applied propensity score matching methods. Among > 3000 patients, propensity matching yielded 139 patients who received AC and 417 patients who did not receive treatment with balanced variables between the groups. Results suggest that AC alone is unlikely to be protective for COVID-19-related morbidity and mortality ([Tremblay 2020](#)).

There is also a quite controversial debate about a possible correlation between the use of ibuprofen and the increased risk of VTE development. According to a recent review ([Arjomandi 2020](#)), the causation between the effects of ibuprofen and VTE remains speculative. The role of ibuprofen on a vascular level remains unclear as well as whether ibuprofen is able to interact with SARS-CoV-2 mechanistically. However, the authors recommend careful considerations on avoiding high dosage of ibuprofen in subjects at particular risk of thromboembolic events.

Neurologic symptoms

Neuroinvasive propensity has been demonstrated as a common feature of human coronaviruses. Viral neuroinvasion may be achieved by several routes, including trans-synaptic transfer across infected neurons, entry via the olfactory nerve, infection of vascular endothelium, or leukocyte migration across the blood-brain barrier (reviews: [Zubair 2020](#), [Ellul 2020](#)). With regard to SARS-CoV-2, early occurrences such as olfactory symptoms (see

above) should be further evaluated for CNS involvement. Potential late neurological complications in cured COVID-19 patients are possible (Baig 2020). In a study of 4491 hospitalized COVID-19 patients in New York City, 606 (13.5%) developed a new neurologic disorder (Frontera 2020). The most common diagnoses were: toxic/metabolic encephalopathy (6.8%, temporary/reversible changes in mental status in the absence of focal neurologic deficits or primary structural brain disease, excluding patients in whom sedative or other drug effects or hypotension explained this), seizure (1.6%), stroke (1.9%), and hypoxic/ischemic injury (1.4%). Whether these more non-specific symptoms are manifestations of the disease itself remains to be seen. There are several observational series of specific neurological features such as Guillain-Barré syndrome (Toscano 2020), myasthenia gravis (Restivo 2020) or Miller Fisher Syndrome and polyneuritis cranialis (Gutierrez-Ortiz 2020).

Especially in patients with severe COVID-19, neurological symptoms are common. In an observational series of 58 patients, ARDS due to SARS-CoV-2 infection was associated with encephalopathy, prominent agitation and confusion, and corticospinal tract signs. Patients with COVID-19 might experience delirium, confusion, agitation, and altered consciousness, as well as symptoms of depression, anxiety, and insomnia (review: Rogers 2020). It remains unclear which of these features are due to critical illness-related encephalopathy, cytokines, or the effect or withdrawal of medication, and which features are specific to SARS-CoV-2 infection (Helms 2020). However, in a large retrospective cohort study comparing 1,916 COVID-19 patients and 1,486 influenza patients (with emergency department visits or hospitalizations), there were 31 acute ischemic strokes with COVID-19, compared to 3 with influenza (Merkler 2020). After adjustment for age, sex, and race, the likelihood of stroke was almost 8-fold higher with COVID-19 (odds ratio, 7.6).

Of note, there is no clear evidence for CNS damage directly caused by SARS-CoV-2. In a study on 21 *cerebrospinal fluid* (CSF) samples from patients with confirmed COVID-19, all were negative. These data suggest that, although SARS-CoV-2 is able to replicate in neuronal cells *in vitro*, SARS-CoV-2 testing in CSF is not relevant in the general population (Destras 2020). In a large post-mortem examination, SARS-CoV-2 could be detected in the brains of 21 (53%) of 40 examined patients but was not associated with the severity of neuropathological changes (Matschke 2020) which seemed to be mild, with pronounced neuroinflammatory changes in the brainstem being the most common finding. In another study, brain specimens obtained from 18 patients who died 0 to 32 days after the onset of symptoms showed only hypoxic changes and did not show encephalitis or other specific brain changes referable to the virus (Solomon 2020).

Dermatological symptoms

Numerous studies have reported on cutaneous manifestations seen in the context of COVID-19. The most prominent phenomenon, the so-called “COVID toes”, are chilblain-like lesions which mainly occur at acral areas. [Chilblain: Frostbeule (de), engelure (fr), sabañón (es), gelone (it), frieira (pt), 冻疮 (cn)] These lesions can be painful (sometimes itchy, sometimes asymptomatic) and may represent the only symptom or late manifestations of SARS-CoV-2 infection. Of note, in most patients with “COVID toes”, the disease is only mild to moderate. It is speculated that the lesions are caused by inflammation in the walls of blood vessels, or by small micro-clots in the blood. However, whether “COVID toes” represent a coagulation disorder or a hypersensitivity reaction is not yet known. Key studies:

- Two different patterns of acute acro-ischemic lesions can overlap ([Fernandez-Nieto 2020](#)). The chilblain-like pattern was present in 95 patients (72.0%). It is characterized by red to violet macules, plaques and nodules, usually at the distal aspects of toes and fingers. The erythema multiform-like pattern was present in 37 patients (28.0%).
- Five clinical cutaneous lesions are described ([Galvan 2020](#)): acral areas of erythema with vesicles or pustules (pseudo-chilblain) (19%), other vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%) and livedo or necrosis (6%). Vesicular eruptions appear early in the course of the disease (15% before other symptoms). The pseudo-chilblain pattern frequently appears late in the evolution of COVID-19 disease (59% after other symptoms).
- In a case series on 22 adult patients with varicella-like lesions ([Marzano 2020](#)), typical features were constant trunk involvement, usually scattered distribution and mild or absent pruritus, the latter being in line with most viral exanthems but not like true varicella. Lesions generally appeared 3 days after systemic symptoms and disappeared by day 8.
- Three cases of COVID-19 associated ulcers in the oral cavity, with pain, desquamative gingivitis, and blisters ([Martin Carreras-Presas 2020](#)).

Other case reports include digitate papulosquamous eruption ([Sanchez 2020](#)), petechial skin rash ([Diaz-Guimaraens 2020](#), [Quintana-Castanedo 2020](#)). However, it should be kept in mind that not all rashes or cutaneous manifestations seen in patients with COVID-19 can be attributed to the virus. Co-infections or medical complications have to be considered. Newer studies reporting in negative PCR and serology have questioned a direct association between acral skin disease and COVID-19:

- Of 31 patients (mostly teenagers) who had recently developed chilblains, histopathologic analysis of skin biopsy specimens (22 patients) confirmed the diagnosis of chilblains and showed occasional lymphocytic or microthrombotic phenomena. In all patients, PCR and serology remained negative ([Herman 2020](#)).
- Among 40 young patients with chilblain lesions and with suspected SARS-CoV-2 infection, serology was positive in 12 (30%). All had negative PCR results at the time of presentation, suggesting that in young patients SARS-CoV-2 is completely suppressed before a humoral immune response is induced ([Hubiche 2020](#)).
- In a cohort series from Valencia following 20 patients aged 1 to 18 years with new-onset acral inflammatory lesions, all lacked systemic manifestations of COVID-19. Surprisingly, both PCR and serologic test results were negative for SARS-CoV-2 ([Roca-Ginés 2020](#)).

Comprehensive mucocutaneous examinations, analysis of other systemic clinical features or host characteristics, and histopathologic correlation, will be vital to understanding the pathophysiologic mechanisms of what we are seeing on the skin (Review: [Madigan 2020](#)).

Kidneys

SARS-CoV-2 has an organotropism beyond the respiratory tract, including the kidneys and the liver. Researchers have quantified the SARS-CoV-2 viral load in precisely defined kidney compartments obtained with the use of tissue micro-dissection from 6 patients who underwent autopsy ([Puelles 2020](#)). Three of these 6 patients had a detectable SARS-CoV-2 viral load in all kidney compartments examined, with preferential targeting of glomerular cells. Renal tropism is a potential explanation of commonly reported clinical signs of kidney injury in patients with COVID-19, even in patients with SARS-CoV-2 infection who are not critically ill ([Zhou 2020](#)). Recent data indicate that renal involvement is more frequent than described in early studies ([Gabarre 2020](#)). Of the first 1,000 patients presenting at the NewYork-Presbyterian/Columbia University, 236 were admitted or transferred to intensive care units ([Argenziano 2020](#)). Of these, 78.0% (184/236) developed acute kidney injury and 35.2% (83/236) needed dialysis. Concomitantly, 13.8% of all patients and 35.2% of patients in intensive care units required in-patient dialysis, leading to a shortage of equipment needed for dialysis and continuous renal replacement therapy.

In recent months, some case reports of collapsing glomerulopathy akin to those seen during the HIV epidemic have been published. All of these cases were in patients of African ethnicity (Velez 2020).

Liver

One of the largest studies, evaluating liver injury in 2273 SARS-CoV-2 positive patients, found that 45% had mild, 21% moderate, and 6.4% severe liver injury. In a multivariate analysis, severe acute liver injury was significantly associated with elevated inflammatory markers including ferritin and IL-6. Peak ALT was significantly associated with death or discharge to hospice (OR 1.14, $p = 0.044$), controlling for age, body mass index, diabetes, hypertension, intubation, and renal replacement therapy (Phipps 2020). In another meta-analysis of 9 studies with a total of 2115 patients, patients with COVID-19 with liver injury were at an increased risk of severity (OR 2.57) and mortality (1.66).

Ocular and atypical manifestations

Ocular manifestations are also common. In a case series from China, 12/38 patients (32%, more common in severe cases) had ocular manifestations consistent with conjunctivitis, including conjunctival hyperemia, chemosis, epiphora, or increased secretions. Two patients had positive PCR results from conjunctival swabs (Wu 2020). The retina can also be affected, as has been shown using optical coherence tomography (OCT), a non-invasive imaging technique that is useful for demonstrating subclinical retinal changes. Twelve adult patients showed hyper-reflective lesions at the level of the ganglion cell and inner plexiform layers more prominently at the papillomacular bundle in both eyes. Since their initial report, the authors have extended their findings to more than 150 patients, demonstrating an absence of blood flow within the retinal lesions of “many” patients (Marinho 2020).

Other new and sometimes puzzling clinical presentations have emerged (and will emerge) in the current pandemic. There are case reports of non-specific symptoms, especially in the elderly population, underlining the need for extensive testing in the current pandemic (Nickel 2020).

Laboratory findings

The most evident laboratory findings in the first large cohort study from China (Guan 2020) are shown in Table 2. On admission, lymphocytopenia was present in 83.2% of the patients, thrombocytopenia in 36.2%, and leukopenia in 33.7%. In most patients, C-reactive protein was elevated to moderate levels;

less common were elevated levels of alanine aminotransferase and D-dimer. Most patients have normal procalcitonin on admission.

Table 2. Percentage of symptoms in first large cohort study from China (Guan 2020). Disease severity was classified according to American Thoracic Society (Metlay 2019) guidelines

Clinical symptoms	All	Severe Disease	Non-Severe
Fever, %	88.7	91.9	88.1
Cough, %	67.8	70.5	67.3
Fatigue, %	38.1	39.9	37.8
Sputum production, %	33.7	35.3	33.4
Shortness of breath, %	18.7	37.6	15.1
Myalgia or arthralgia, %	14.9	17.3	14.5
Sore throat, %	13.9	13.3	14.0
Headache, %	13.6	15.0	13.4
Chills, %	11.5	15.0	10.8
Nausea or vomiting, %	5.0	6.9	4.6
Nasal congestion, %	4.8	3.5	5.1
Diarrhea, %	3.8	5.8	3.5
Radiological findings			
Abnormalities on X-ray, %	59.1	76.7	54.2
Abnormalities on CT, %	86.2	94.6	84.4
Laboratory findings			
WBC < 4,000 per mm ³ , %	33.7	61.1	28.1
Lymphocytes < 1,500 per mm ³ , %	83.2	96.1	80.4
Platelets < 150,000 per mm ³ , %	36.2	57.7	31.6
C-reactive protein ≥ 10 mg/L, %	60.7	81.5	56.4
LDH ≥ 250 U/L, %	41.0	58.1	37.1
AST > 40 U/L, %	22.2	39.4	18.2
D-dimer ≥ 0.5 mg/L, %	46.6	59.6	43.2

Inflammation

Parameters indicating inflammation such as elevated CRP and procalcitonin are very frequent findings. They have been proposed to be important risk factors for disease severity and mortality (Chen 2020). For example, in a multivariate analysis of a retrospective cohort of 1590 hospitalized subjects with COVID-19 throughout China, a procalcitonin > 0.5 ng/ml at admission had a HR for mortality of 8.7 (95% CI: 3.4-22.3). In 359 patients, CRP performed better than other parameters (age, neutrophil count, platelet count) in predicting adverse outcome. Admission serum CRP level was identified as a moderate discriminator of disease severity (Lu 2020). Of 5279 cases confirmed in a large

medical center in New York, 52% of them admitted to hospital, a CRP > 200 was more strongly associated (odds ratio 5.1) with critical illness than age or comorbidities (Petrilli 2019).

Some studies have suggested that the dynamic change of interleukin-6 (IL-6) levels and other cytokines can be used as a marker in disease monitoring in patients with severe COVID-19 (Chi 2020, Zhang 2020). In a large study of 1484 patients, several cytokines were measured upon admission to the Mount Sinai Health System in New York (Del Valle 2020). Even when adjusting for disease severity, common laboratory inflammation markers, hypoxia and other vitals, demographics, and a range of comorbidities, IL-6 and TNF- α serum levels remained independent and significant predictors of disease severity and death. These findings were validated in a second cohort of 231 patients. The authors propose that serum IL-6 and TNF- α levels should be considered in the management and treatment of patients with COVID-19 to stratify prospective clinical trials, guide resource allocation and inform therapeutic options.

There is also one study suggesting that serum cortisol concentration seems to be a better independent predictor than other laboratory markers associated with COVID-19, such as CRP, D-dimer, and neutrophil to leukocyte ratio (Tan 2020).

Hematological: Lymphocytes, platelets, RDW

Lymphocytopenia and transient but severe T cell depletion is a well-known feature of SARS (He 2005). In COVID-19, lymphopenia is also among the most prominent hematological features. Lymphopenia may be predictive for progression (Ji 2020) and patients with severe COVID-19 present with lymphocytopenia of less than 1500/ μ l in almost 100% of cases (Guan 2020). It's not only the total lymphocyte count. There is growing evidence for a transient depletion of T cells. Especially the reduced CD4+ and CD8+ T cell counts upon admission were predictive of disease progression in a larger study (Zhang 2020). In another large study on COVID-19 patients, CD3+, CD4+ and CD8+ T cells as well as NK cells were significantly decreased in COVID-19 patients and related to the severity of the disease. According to the authors, CD8+ T cells and CD4+ T cell counts can be used as diagnostic markers of COVID-19 and predictors of disease severity (Jiang 2020). Beside T cells, B cells may also play a role. In 104 patients, a decrease in B cells was independently associated with prolonged viral RNA shedding (Hao 2020).

Another common hematological finding is low platelet counts that may have different causes (Review: Xu 2020). A meta-analysis of 24 studies revealed a weighted incidence of thrombocytopenia in COVID-19 patients of 12.4% (95%

CI 7.9%–17.7%). The meta-analysis of binary outcomes (with and without thrombocytopenia) indicated an association between thrombocytopenia and a 3-fold enhanced risk of a composite outcome of ICU admission, progression to acute respiratory distress syndrome, and mortality (Zong 2020). Cases of hemorrhagic manifestation and severe thrombocytopenia responding to immunoglobulins fairly quickly with a sustained response over weeks have been reported (Ahmed 2020).

Red blood cell distribution width (RDW) is another component of complete blood counts that quantifies the variation of individual red blood cell (RBC) volumes and has been shown to be associated with elevated risk for morbidity and mortality in a wide range of diseases. In a large cohort study including 1641 adults diagnosed with SARS-CoV-2 infection and admitted to 4 hospitals in Boston (Foy 2020), RDW was associated with mortality risk in Cox models (hazard ratio of 1.09 per 0.5% RDW increase and 2.01 for an RDW > 14.5% vs ≤ 14.5%).

However, there are also cohorts in which hematological parameters such as thrombocytes, neutrophil-to-lymphocyte ratio or D-dimers do not allow prediction of patient outcome (Pereyra 2020). These routine parameters, despite giving guidance on the overall health of the patient, might not always accurately indicate COVID-19-related complications.

Cardiac: Troponin

Given the cardiac involvement especially in severe cases (see above), it is not surprising that cardiac parameters are frequently elevated. A meta-analysis of 341 patients found that cardiac troponin I levels are significantly increased only in patients with severe COVID-19 (Lippi 2020). In 179 COVID-19 patients, cardiac troponin ≥ 0.05 ng/mL was predictive of mortality (Du 2020). Among 2736 COVID-19 patients admitted to one of five hospitals in New York City who had troponin-I measured within 24 hours of admission, 985 (36%) patients had elevated troponin concentrations. After adjusting for disease severity and relevant clinical factors, even small amounts of myocardial injury (0.03–0.09 ng/mL) were significantly associated with death (adjusted HR: 1.75, 95% CI 1.37–2.24) while greater amounts (> 0.09 ng/dL) were significantly associated with higher risk (adjusted HR 3.03, 95% CI 2.42–3.80). However, it remains to be seen whether troponin levels can be used as a prognostic factor. A comprehensive review on the interpretation of elevated troponin levels in COVID-19 has been recently published (Chapman 2020).

Coagulation: D-dimer, aPTT

Several studies have evaluated the coagulation parameter D-dimer in the progression of COVID-19. Among 3334 consecutive patients admitted to 4 hospitals at New York City, a thrombotic event occurred in 16.0%. D-dimer level at presentation was independently associated with thrombotic events, consistent with early coagulopathy (Bilaloglu 2020). In the Wuhan study, all patients surviving had low D-dimer during hospitalization, whereas levels in non-survivors tended to increase sharply at day 10. In a multivariate analysis, D-dimer of $> 1 \mu\text{g/mL}$ remained the only lab finding which was significantly associated with in-hospital death, with an odds ratio of 18.4 (2.6-129, $p = 0.003$). However, D-dimer has a reported association with mortality in patients with sepsis and many patients died from sepsis (Zhou 2020).

In a considerable proportion of patients, a prolonged aPTT can be found. Of 216 patients with SARS-CoV-2, this was the case in 44 (20%). Of these, 31/34 (91%) had positive lupus anticoagulant assays. As this is not associated with a bleeding tendency, it is recommended that prolonged aPTT should not be a barrier to the use of anti-coagulation therapies in the prevention and treatment of venous thrombosis (Bowles 2020). Another case series of 22 patients with acute respiratory failure present a severe hypercoagulability rather than consumptive coagulopathy. Fibrin formation and polymerization may predispose to thrombosis and correlate with a worse outcome (Spiezia 2020).

Lab findings as risk factor

It is not very surprising that patients with severe disease had more prominent laboratory abnormalities than those with non-severe disease. It remains unclear how a single parameter can be of clinical value as almost all studies were retrospective and uncontrolled. Moreover, the numbers of patients were low in many studies. However, there are some patterns which may be helpful in clinical practice. Lab risk factors are:

- Elevated CRP, procalcitonin, interleukin-6 and ferritin
- Lymphocytopenia, CD4 T cell and CD8 T cell depletion, leukocytosis
- Elevated D-dimer and troponin
- Elevated LDH

Clinical classification

There is no broadly accepted or valid clinical classification for COVID-19. The first larger clinical study distinguished between severe and non-severe cases (Guan 2020), according to the Diagnosis and Treatment Guidelines for Adults

with Community-acquired Pneumonia, published by the American Thoracic Society and Infectious Diseases Society of America (Metlay 2019). In these validated definitions, severe cases include either one major criterion or three or more minor criteria. Minor criteria are a respiratory rate > 30 breaths/min, $\text{PaO}_2/\text{FIO}_2$ ratio < 250 , multilobar infiltrates, confusion/disorientation, uremia, leukopenia, low platelet count, hypothermia, hypotension requiring aggressive fluid resuscitation. Major criteria comprise septic shock with need for vasopressors or respiratory failure requiring mechanical ventilation.

Some authors (Wang 2020) have used the following classification including four categories:

1. Mild cases: clinical symptoms were mild without pneumonia manifestation through image results
2. Ordinary cases: having fever and other respiratory symptoms with pneumonia manifestation through image results
3. Severe cases: meeting any one of the following: respiratory distress, hypoxia ($\text{SpO}_2 \leq 93\%$), abnormal blood gas analysis: ($\text{PaO}_2 < 60\text{mmHg}$, $\text{PaCO}_2 > 50\text{mmHg}$)
4. Critical cases: meeting any one of the following: Respiratory failure which requires mechanical ventilation, shock, accompanied by other organ failure that needs ICU monitoring and treatment.

In the report of the Chinese CDC, estimation of disease severity used almost the same categories (Wu 2020) although numbers 1 and 2 were combined. According to the report, there were 81% mild and moderate cases, 14% severe cases and 5% critical cases. There are preliminary reports from the Italian National Institute of Health, reporting on 24.9% severe and 5.0% critical cases (Livingston 2020). However, these numbers are believed to strongly overestimate the disease burden, given the very low number of diagnosed cases in Italy at the time. Among 7,483 US health care workers with COVID-19, a total of 184 (2.1–4.9%) had to be admitted to ICUs. Rate was markedly higher in HCWs > 65 years of age, reaching 6.9–16.0% (CDC 2020).

Outcome

We are facing rapidly increasing numbers of severe and fatal cases in the current pandemic. The two most difficult but most frequently asked clinical questions are 1. How many patients end up with severe or even fatal courses of COVID-19? 2. What is the true proportion of asymptomatic infections? We will learn more about this shortly through serological testing studies. Howev-

er, it will be important that these studies are carefully designed and carried out, especially to avoid bias and confounding.

Case fatality rates (CFR)

The country-specific crude case fatality rates (CFR), the percentage of COVID-19-associated deaths among confirmed SARS-CoV-2 infections, have been the subject of much speculation. There are still striking differences between countries. According to [worldometer.com](https://www.worldometer.com) assessed on October 12, 2020, the crude CFR between the 100 most affected countries (in terms of absolute numbers) ranged from 0.05 (Singapore) to 10.2 (Mexico). Within the 10 most affected countries in Europe, the CFR range was between 0.8% (Czechia) and 10.2% (Italy).

Although it is well known that the CFR of a disease can be biased by detection, selection or reporting ([Niforatos 2020](#)), and although it became quickly clear that older age is a major risk factor for mortality (see below), many other factors contributing to regional differences throughout the world have been discussed in recent months. These factors include not only differences in the overall age structure of the general population of a country and co-residence patterns, but also co-morbidity burden, obesity prevalence and smoking habits as well as societal and social psychological factors. Others include heterogeneity in testing and reporting approaches, variations in health care system capacities and health care and even political regime. Different virus strains or even environmental factors such as air pollution have also been discussed, as well as potential differences in genetic variability or even “trained immunity” induced by certain live vaccines such as bacillus Calmette-Guérin (for references see [Hoffmann C 2020](#)).

We can probably exclude most of these speculations. SARS-CoV-2 is not deadlier in Italy (CFR 10.2%), United Kingdom (7.1%), or Sweden (6.0%), compared to Slovakia (0.3%), Israel (0.8%), India (1.5%) or USA (2.7%). Instead, there are three major factors that have to be taken into account:

- The age of the pandemic, especially of the population *which is first affected*. Data from the 20 most affected European countries and the USA and Canada show that the variance of crude CFR of COVID-19 is predominantly (80-96%) determined by the proportion of older individuals who are diagnosed with SARS-CoV-2 ([Hoffmann C 2020](#)). Of note, the age distribution of SARS-CoV-2 infections is still far from homogeneous. The proportion of individuals older than 70 years among confirmed SARS-CoV-2 cases still differs markedly between the countries, ranging from 5% to 40% (Figure 1).

Countries' testing policies (and capacities). The fewer people you test (all people, only symptomatic patients, only those with severe symptoms), the higher the mortality. In Germany, for example, testing systems and high lab capacities were established rapidly, within weeks in January (Stafford 2020).

- Stage of the epidemic. Some countries have experienced their first (or second) waves early while others lagged a few days or weeks behind. Death rates only reflect the infection rate of the previous 2 to 4 weeks.

There is no doubt that the marked variation of CFR across countries will diminish over time, for example, if less affected countries such as Korea or Singapore fail to protect their older age groups; or if countries with high rates at the beginning (such as Italy, Belgium or Sweden) start to implement broad testing in younger age groups. This process has already begun. In Belgium, for example, CFR peaked on May 11 with an appalling rate of 16.0%; it has now dropped to 6.3%. The CFR in the USA peaked on May 16 (6.1%) and is now less than half that. Germany started with a strikingly low CFR of 0.2% by the end of March (prompting much attention even in scientific papers), peaked on June 18 (4.7%) and is now (October 10) at 3.0%.

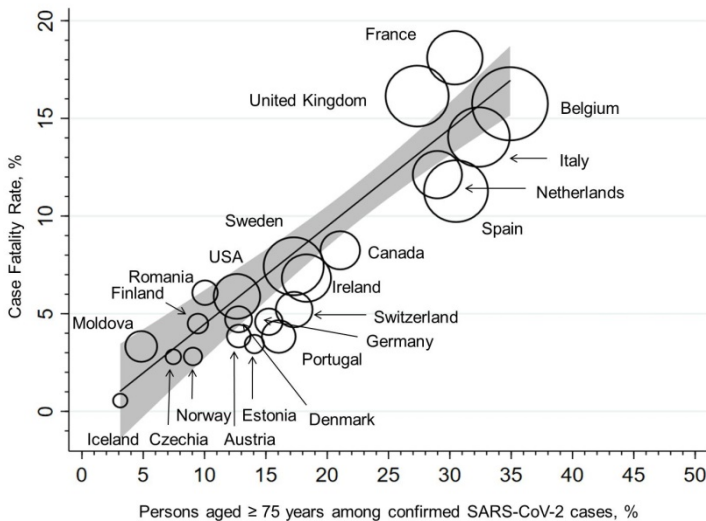


Figure 1. Association between case fatality rate (CFR) and the proportion of persons over 75 years of age among all confirmed SARS-CoV-2 cases ($R^2=0.8034$, $p<0.0001$). The circle sizes reflect the country-specific numbers of COVID-19 associated deaths per million habitants; the linear fit prediction plot with a 95% confidence interval was estimated by weighted linear regression (weight = total number of COVID-19 associated deaths).

CFR among health care workers, well-defined populations

In well-monitored populations in which under-reporting is unlikely or can be largely determined, the mortality rates may better reflect the “true” CFR of COVID-19. This applies to healthcare workers (HCW) but also to populations of “well-defined” (limited) outbreaks and in populations with available serology data. The low mortality rates in these populations are remarkable.

- In a large study of 3387 HCW from China infected with SARS-CoV-2, only 23 died, corresponding to a mortality rate of 0.68%. The median age was 55 years (range, 29 to 72), and 11 of the 23 deceased HCW had been reactivated from retirement ([Zhan 2020](#)). Current studies in the US have found similar mortality estimates of 0.3-0.6% ([CDC 2020](#)). Of the 27 HCW who died from COVID-19 until mid-April, 18 were over 54 years of age. The overall low mortality rates were probably due to the fact that HCWs were younger and healthier, but also that they had been tested earlier and more frequently.
- On the cruise ship Diamond Princess, as of May 31, the total number of infected reached 712, and 13 patients died from the disease leading to a CFR of 1.8% ([Moriarty 2020](#)). Of note, around 75% of the patients on the Diamond Princess were 60 years or older, many of them in their eighties. Projecting the Diamond Princess CFR onto the age structure of the general population, mortality would be in a range of 0.2-0.4%.
- According to an investigation of the shore-based USS Theodore Roosevelt outbreak, only 6/736 infected sailors were hospitalized, and one (a “senior listed member in his 40s”) died during the study period (CFR 0.1%) ([Alvarado 2020](#)).
- Using population-based seroprevalences in Geneva (Switzerland) and after accounting for demography, the population-wide infection fatality rate (IFR) was 0.64% (0.38–0.98) ([Perez-Saez 2020](#)).

CFR compared to influenza

More time and data are needed before the COVID-19 pandemic can be accurately compared with past pandemics. But what makes SARS-CoV-2 different from pandemic influenza virus? It's not only that SARS-CoV-2 is a new pathogen and influenza is not and that the diseases differ clinically. The picture is more complex. It also depends on which flu season you are talking about – the influenza pandemic excess mortality ranged from extreme (1918) to mild (2009) over the past 100 years. Another key difference between SARS-CoV-2 and pandemic influenza is the age distribution of patients who are severely

ill. Mortality due to SARS-CoV-2 and SARS-CoV is strongly skewed towards people older than 70 years, very dissimilar to the 1918 and 2009 influenza pandemics.

Pooled estimates of all-cause mortality for 24 European countries for the period March–April 2020 showed that excess mortality of COVID-19 particularly affected ≥ 65 -year-olds (91% of all excess deaths) and to a far lesser extent those 45–64 (8%) and 15–44-year-olds (1%) (Vestergaard 2020). The excess mortality of COVID-19 is markedly higher than for major influenza pandemics in the past. For example, the 2009 pandemic influenza A H1N1 globally led to 201,200 respiratory deaths (range 105,700–395,600) with an additional 83,300 cardiovascular deaths (Dawood 2012). This is by far lower than the deaths caused by COVID-19 to date. According to a recent review, the population risk of admission to the intensive care unit is five to six times higher in patients infected with SARS-CoV-2 than in those with the fairly mild 2009 influenza pandemic (Petersen 2020).

In New York City, a study analyzed standardized mortality ratios (SMR) of comparator pandemics and epidemics relative to the first 2020 wave of COVID-19 (Muscatello 2020). In older people, COVID-19 mortality until June 2020 was more than 10-fold higher than a severe influenza season, and more than 300-fold higher than the 2009–10 influenza pandemic. Compared to the catastrophic 1918–19 winter wave of the influenza pandemic, there are marked differences for different age groups. The 1918–19 influenza had a high mortality, especially in younger persons (5–15 years; $\sim 25\%$ of total deaths), possibly due to antibody-dependent enhancement and ‘cytokine storms’ in younger people but also due to some protective cross-immunity from previous influenza outbreaks among those older. Compared to COVID-19, the overall age-adjusted, all-age mortality rate of the influenza 1918–19 was 6.7 times higher. In younger people (< 45 years), the SMR was 42; that is, 42 times higher for influenza in 1918–19 than for COVID-19. However, in people older than 44 years of age, the SMR was 0.56; that is, 44% lower in 1918–19 than for COVID-19.

Modeling scenarios without appropriate mitigation measures, simulations predict incredibly high peaks in active cases and alarmingly high numbers of deaths far into the future. In Germany, for example, 32 million total infections would result in 730,000 deaths over the course of the epidemic, which would seem to occur only by the end of the summer 2021 under the assumption that no reliable treatment is available before then (Barbarossa 2020).

Older Age

From the beginning of the epidemic, older age has been identified as an important risk factor for disease severity (Huang 2020, Guan 2020). In Wuhan, there was a clear and considerable age dependency in symptomatic infections (susceptibility) and outcome (fatality) risks, by multiple folds in each case (Wu 2020). The summarizing report from the Chinese CDC found a death rate of 2.3%, representing 1023 among 44,672 confirmed cases (Wu 2020). Mortality increased markedly in older people. In cases aged 70 to 79 years, CFR was 8.0% and cases in those aged 80 years older had a 14.8% CFR. There is now growing data from serology-informed estimates that the same is true for the infection fatality risk (IFR). After accounting for demography and age-specific seroprevalence, IFR was 0.0092% (95% CI 0.0042–0.016) for individuals aged 20–49 years, 0.14% (0.096–0.19) for those aged 50–64 years but 5.6% (4.3–7.4) for those aged 65 years and older (Perez-Saez 2020).

In recent months, these data have been confirmed by almost all studies published throughout the world. In almost all countries, age groups of 60 years or older contribute to more than 90% of all death cases.

- In a large registry analysing the epidemic in the UK in 20,133 patients, the median age of the 5165 patients (26%) who died in hospital from COVID-19 was 80 years (Docherty 2020).
- Among 1591 patients admitted to ICU in Lombardy, Italy, older patients (> 63 years) had markedly higher mortality than younger patients (36% vs 15%). Of 362 patients older than 70 years of age, mortality was 41% (Grasselli 2020).
- According to the Italian National Institute of Health, an analysis of the first 2003 death cases, median age was 80.5 years. Only 17 (0.8%) were 49 years or younger, and 88% were older than 70 years (Livingston 2020).
- Detailed analysis of all-cause mortality at Italian hot spots showed that the deviation in all-cause deaths compared to previous years during epidemic peaks was largely driven by the increase in deaths among older people, especially in men (Piccininni 2020, Michelozzi 2020).
- In 5700 patients admitted to New York hospitals, there was a dramatic increase of mortality among older age groups, reaching 61% (122/199) in men and 48% (115/242) in women over 80 years of age (Richardson 2020).
- The median age of 10,021 adult COVID-19 patients admitted to 920 German hospitals was 72 years. Mortality was 53% in patients being mechanically ventilated (n=1727), reaching 63% in patients aged 70–79 years and 72% in patients aged 80 years and older (Karagiannidis 2020).

- In an outbreak reported from King County, Washington, a total of 167 confirmed cases was observed in 101 residents (median age 83 years) of a long-term care facility, in 50 healthcare workers (HCW, median age 43 years), and 16 visitors. The case fatality rate was 33.7% among residents and 0% among HCW ([McMichael 2020](#)).

There is no doubt that older age is by far the most important risk factor for mortality. Countries failing to protect their elderly population for different reasons (such as Italy, Belgium or Sweden) are facing a higher CFR, while those without many older patients infected by SARS-CoV-2 (such as the Republic of Korea, Singapore, Australia) have markedly lower rates.

What are the reasons? Severe endothelial injury as seen in critically ill patients ([Ackermann 2020](#)) and endotheliopathy is an essential part of the pathological response to severe COVID-19, leading to respiratory failure, multi-organ dysfunction and thrombosis ([Goshua 2020](#)). Circulating endothelial cells are a marker of endothelial injury in severe COVID-19 ([Guervilly 2020](#)) and there is a direct and rapid cytotoxic effect of plasma collected from critically ill patients on vascular endothelial cells ([Rauch 2020](#)). It is therefore tempting to speculate that endothelial injury will be particularly harmful in older patients with atherosclerosis.

But maybe not all is due to arteriosclerosis. “Inflammaging”, a common denominator of age-associated frailty, may also contribute to the severe COVID-19 course in older people. One hypothesis is that pre-existing inflammatory cells, including senescent populations and adipocytes, create the inflammaging phenotype that amplifies subsequent inflammatory events. Nevertheless, high amounts of inflammation alone do not explain the devastating tissue destruction and it may be that age-associated changes in T cells have a role in the immunopathology (review: [Akbar 2020](#)). There is growing evidence that coordination of SARS-CoV-2 antigen-specific responses is disrupted in older individuals. Scarcity of naive T cells was also associated with ageing and poor disease outcomes ([Rydzynski 2020](#)).

Sex and ethnicity

A striking finding is the lower mortality in female patients, evident through almost all available data. In Italy, for example, male gender was an independent risk factor associated with mortality at ICU with a hazard ratio of 1.57 ([Grasselli 2020](#)). Using a health analytics platform covering 40% of all patients in England, COVID-19-related death was associated with being male, with a hazard ratio of 1.59 (95% CI 1.53–1.65) ([Williamson 2020](#)). The hitherto largest registry study with detailed data on demographics and other clinical factors

is shown in Table 3. There is some evidence that there are sex-specific differences in clinical characteristics and prognosis and that the presence of comorbidities is of less impact in females (Meng 2020). It has been speculated that the higher vulnerability in men is due to the presence of subclinical systemic inflammation, blunted immune system, down-regulation of ACE2 and accelerated biological aging (Bonafè 2020).

Table 3. Age and co-morbidities in a large registry study (Docherty 2020), providing multivariate analyses and hazard ratios.

	UK, n = 15,194
Hazard Ratio (95% CI)	Death
Age 50-59 vs < 50	2.63 (2.06-3.35)
Age 60-69 vs < 50	4.99 (3.99-6.25)
Age 70-79 vs < 50	8.51 (6.85-10.57)
Age > 80 vs < 50	11.09 (8.93-13.77)
Female	0.81 (0.75-0.86)
Chronic cardiac disease	1.16 (1.08-1.24)
Chronic pulmonary disease	1.17 (1.09-1.27)
Chronic kidney disease	1.28 (1.18-1.39)
Hypertension	
Diabetes	1.06 (0.99-1.14)
Obesity	1.33 (1.19-1.49)
Chronic neurological disorder	1.18 (1.06-1.29)
Dementia	1.40 (1.28-1.52)
Malignancy	1.13 (1.02-1.24)
Moderate/severe liver disease	1.51 (1.21-1.88)

An in-depth analysis performed on 137 COVID-19 patients found that male patients had higher plasma levels of innate immune cytokines such as IL-8 and IL-18 along with more robust induction of non-classical monocytes. A poor T cell response negatively correlated with patients' age and was associated with worse disease outcome in male patients, but not in female patients. Conversely, higher innate immune cytokines were associated with worse disease progression in female patients, but not in male patients (Takahashi 2020). Emerging knowledge on the basic biological pathways that underlie gender differences in immune responses needs to be incorporated into research efforts on SARS-CoV-2 pathogenesis and pathology to identify targets for therapeutic interventions aimed at enhancing antiviral immune function

and lung airway resilience while reducing pathogenic inflammation in COVID-19 (review: [Bunders 2020](#)).

Ethnic minorities may be disproportionately affected by the COVID-19 pandemic. Among the first 1.3 million lab-confirmed COVID-19 cases reported to CDC until May 30, 2020, 33% of persons were Hispanic (accounting for 18% of the US population), 22% (13%) were black, and 1.3% (0.7%) were non-Hispanic American Indian or Alaska Native ([Stoke 2020](#)). However, in a large cohort study on 5902 COVID-19 patients treated at a single academic medical center in New York, survival outcomes of non-Hispanic Black and Hispanic patients were at least as good as those of their non-Hispanic White counterparts when controlling for age, sex, and comorbidities ([Kabarriti 2020](#)). Several other US studies have also found no differences, after controlling for confounders such as age, gender, obesity, cardiopulmonary comorbidities, hypertension, and diabetes ([McCarty 2020](#), [Muñoz-Price 2020](#), [Yehia 2020](#)). There is some evidence indicating a longer wait to access care among black patients in the US, resulting in more severe illness on presentation to health care facilities ([Price-Haywood 2020](#)).

Obesity

Several studies have found obesity to be an important risk factor ([Goyal 2020](#), [Petrilli 2019](#)). Among the first 393 consecutive patients who were admitted to two hospitals in New York City, obese patients were more likely to require mechanical ventilation. Obesity was also an important risk factor in France ([Caussy 2020](#)), Singapore and the US, especially in younger patients ([Ong 2020](#), [Anderson 2020](#)). Of 3222 young adults (age 18 to 34 years) hospitalized for COVID-19 in the US, 684 (21%) required intensive care and 88 patients (2.7%) died. Morbid obesity and hypertension were associated with a greater risk of death or mechanical ventilation. Importantly, young adults aged 18 to 34 years with multiple risk factors (morbid obesity, hypertension, and diabetes) faced risks similar to 8862 middle-aged (age 35-64 years) adults without these conditions ([Cunningham 2020](#)). A recent review has described some hypotheses regarding the deleterious impact of obesity on the course of COVID-19 ([Lockhart 2020](#)), summarizing current knowledge on the underlying mechanisms. These are:

1. Increased inflammatory cytokines (potentiate the inflammatory response)
2. Reduction in adiponectin secretion (abundant in the pulmonary endothelium)
3. Increases in circulating complement components

4. Systemic insulin resistance (associated with endothelial dysfunction and with increased plasminogen activator inhibitor-1)
5. Ectopic lipid deposited in type 2 pneumocytes (predisposing to lung injury).

Comorbidities

Besides older age and obesity, many risk factors for severe disease and mortality have been evaluated in the current pandemic.

Early studies from China found comorbidities such as hypertension, cardiovascular disease and diabetes to be associated with severe disease and death (Guan 2020). Among 1,590 hospitalised patients from mainland China, after adjusting for age and smoking status, COPD (hazard ratio, 2.7), diabetes (1.6), hypertension (1.6) and malignancy (3.5) were risk factors for reaching clinical endpoints (Guan 2020). Dozens of further studies have also addressed risk factors (Shi 2020, Zhou 2020). The risk scores that have been mainly proposed by Chinese researchers are so numerous that they cannot be discussed here. They were mainly derived from uncontrolled data and their clinical relevance remains limited. An interactive version of a relatively simple, so called “COVID-19 Inpatient Risk Calculator” (CIRC) evaluated in 787 patients admitted with mild-to-moderate disease between March 4 and April 24 in five US hospitals in Maryland and Washington (Garibaldi 2020), is available at https://rsconnect.biostat.jhsph.edu/covid_predict.

Smoking as a risk factor is under discussion, as well as COPD, kidney diseases and many others (see chapter *Comorbidities*, page 381). Among 1150 adults admitted to two NYC hospitals with COVID-19 in March, older age, chronic cardiac disease (adjusted HR 1.76) and chronic pulmonary disease (2.94) were independently associated with in-hospital mortality (Cummings 2020).

The main problem of all studies published to date is that their uncontrolled data is subject to confounding and they do not prove causality. Even more importantly, the larger the numbers, the more imprecise the definition of a given comorbidity. What is a “chronic cardiac disease”, a mild and well-controlled hypertension or a severe cardiomyopathy? The clinical manifestations and the relevance of a certain comorbidity may be very heterogeneous (see chapter *Comorbidities*, page 381).

There is growing evidence that sociodemographic factors play a role. Many studies did not adjust for these factors. For example, in a large cohort of 3481 patients in Louisiana, US, public insurance (Medicare or Medicaid), residence in a low-income area, and obesity were associated with increased odds of hospital admission (Price-Haywood 2020). A careful investigation of the NYC

epidemic revealed that the Bronx, which has the highest proportion of racial and ethnic minorities, the most persons living in poverty, and the lowest levels of educational attainment, had higher rates (almost two-fold) of hospitalization and death related to COVID-19 than the other 4 NYC boroughs Brooklyn, Manhattan, Queens and Staten Island ([Wadhera 2020](#)).

Taken together, large registry studies have found slightly elevated hazard ratios of mortality for multiple comorbidities (Table 3). It seems, however, that most patients with preexisting conditions are able to control and eradicate the virus. Co-morbidities play a major role in those who do not resolve and who fail to limit the disease to an upper respiratory tract infection and who develop pneumonia. Facing the devastation that COVID-19 can inflict not only on the lungs but on many organs, including blood vessels, the heart and kidneys (nice review: [Wadman 2020](#)), it seems plausible that a decreased cardiovascular and pulmonary capacity impact clinical outcome in these patients.

However, at this time, we can only speculate about the precise role of comorbidities and their mechanisms to contribute to disease severity.

Is there a higher susceptibility? In a large, population-based study from Italy, patients with COVID-19 had a higher baseline prevalence of cardiovascular conditions and diseases (hypertension, coronary heart disease, heart failure, and chronic kidney disease). The incidence was also increased in patients with previous hospitalizations for cardiovascular or non-cardiovascular diseases ([Mancia 2020](#)). A large UK study found some evidence of potential socio-demographic factors associated with a positive test, including deprivation, population density, ethnicity, and chronic kidney disease ([de Lusignan 2020](#)). However, even these well performed studies cannot completely rule out the (probably strong) diagnostic suspicion bias. Patients with co-morbidities could be more likely to present for assessment and be selected for SARS-CoV-2 testing in accordance with guidelines. Given the high number of nosocomial outbreaks, they may also be at higher risk for infection, just due to higher hospitalization rates.

Predisposition

COVID-19 shows an extremely variable course, from completely asymptomatic to fulminantly fatal. In some cases it affects young and apparently healthy people, for whom the severity of the disease is neither caused by age nor by any comorbidities – just think of the Chinese doctor Li Wenliang, who died at the age of 34 from COVID-19 (see chapter *The First 8 Months*, page 431). So far, only assumptions can be made. The remarkable heterogeneity of disease patterns from a clinical, radiological, and histopathological point of view has led

to the speculation that the idiosyncratic responses of individual patients may be in part related to underlying genetic variations. Many single nucleotide polymorphisms (SNPs) across a variety of genes (eg, ACE2, TMPRSS2, HLA, CD147, MIF, IFNG, IL6) have been implicated in the pathology and immunology of SARS-CoV-2 and other pathogenic coronaviruses (Ovsyannikova 2020). The 'COVID-19 Host Genetics Initiative' brings together the human genetics community to generate, share, and analyze data to learn the genetic determinants of COVID-19 susceptibility, severity, and outcomes (CHGI 2020). It seems that regions on chromosome 3 are significantly associated with severe COVID-19 at the genome-wide level. The risk variant in this region confers an odds ratio for requiring hospitalization of 1.6 (95% confidence interval: 1.42-1.79).

Some further key studies are listed here:

- A large study identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with COVID-19 with respiratory failure and confirmed a potential involvement of the ABO blood-group system (Elinghaus 2020). A higher risk in blood group A was found compared to other blood groups (odds ratio, 1.45; 95% CI, 1.20 to 1.75) and a protective effect in blood group O as compared with other blood groups (odds ratio, 0.65; 95% CI, 0.53 to 0.79)
- In a meta-analysis of 7 studies, comparing 7503 SARS-CoV-2 positive patients with 2,962,160 controls, SARS-CoV-2 positive individuals were more likely to have blood group A (pooled OR 1.23, 95% CI: 1.09–1.40) and less likely to have blood group O (pooled OR 0.77, 95% CI: 0.67–0.88) (Golinelli 2020).
- Associations between ApoEε4 alleles and COVID-19 severity, using the UK Biobank data (Kuo 2020). ApoEε4ε4 homozygotes were more likely to be COVID-19 test positives (odds ratio 2.31, 95% CI: 1.65-3.24) compared to ε3ε3 homozygotes. The ApoEε4ε4 allele increased risks of severe COVID-19 infection, independent of pre-existing dementia, cardiovascular disease, and type 2 diabetes.
- A report from Iran describes three brothers aged 54 to 66 who all died of COVID-19 after less than two weeks of fulminating progress. All three had previously been healthy, without underlying illnesses (Yousefzadegan 2020).
- Two families with rare germline variants in an innate immune-sensing gene, toll-like receptor 7 (TLR7), that leads to severe disease even in young males who inherit the mutated gene on a single copy of their X chromosome (van der Made 2020).

In addition to the genetic predisposition, other potential reasons for a severe course need to be considered: the amount of viral exposure (probably high for Li Wenliang?), the route by which the virus enters the body, ultimately also the virulence of the pathogen and a possible (partial) immunity from previous viral diseases. If you inhale large numbers of virus deeply, leading rapidly to a high amount of virus in the pulmonary system, this may be much worse than smearing a small amount of virus on your hand and, later, to your nose. In this latter case, the immune system in the upper respiratory tract may have much more time to limit further spread into the lungs and other organs. After an outbreak at a Swiss Army base, soldiers had to keep a distance of at least 2 m from each other at all times, and in situations where this could not be avoided (e.g., military training), they had to wear a surgical face mask. Of the 354 soldiers infected prior to the implementation of social distancing, 30% fell ill from COVID-19. While no soldier in a group of 154 in which infections appeared after implementation of social distancing developed COVID-19 (Bielecki 2020).

Pre-existing SARS-CoV-2 S-reactive T cells may also play a role, contributing to the divergent manifestations of COVID-19. These cells represent cross-reactive clones, probably acquired during previous infections with endemic human coronaviruses (HCoVs). In healthy SARS-CoV-2-unexposed donors, they were found in 35% (Braun 2020). However, the clinical effect of these T cells and other immunological factors on clinical outcomes remains to be determined. There are hundreds of immunological papers focusing on the unresolved question why some patients develop severe disease, while others do not (review: Gutierrez 2020). It remains also to be seen whether T cells provide long-term protection from reinfection with SARS-CoV-2 and if there is a natural immunity, induced by cross-reactive T cells (Le Bert 2020, Mateus 2020).

Over the coming months, we will get a clearer view of 1) correlates of immunoprotection, such as virus-specific antibodies that limit disease and 2) correlates of immune dysregulation, such as cytokine over-production that may promote disease.

Overburdened health care systems

Mortality may be also higher in situations where hospitals are unable to provide intensive care to all the patients who need it, in particular ventilator support. Mortality would thus also be correlated with health-care burden. Preliminary data show clear disparities in mortality rates between Wuhan (> 3%), different regions of Hubei (about 2.9% on average), and across the other provinces of China (about 0.7% on average). The authors have postulated that

this is likely to be related to the rapid escalation in the number of infections around the epicenter of the outbreak, which resulted in an insufficiency of health-care resources, thereby negatively affecting patient outcomes in Hubei, while this was not the case in other parts of China (Ji 2020). Another study estimated the risk of death in Wuhan as high as 12% in the epicentre and around 1% in other more mildly affected areas (Mizumoto 2020).

Finally, there may be differences between hospitals. In a US cohort of 2215 adults with COVID-19 who were admitted to ICUs at 65 sites, 784 (35.4%) died within 28 days. However, mortality showed a wide variation between hospitals (range, 6.6%-80.8%). One of the well known factors associated with death was a hospital with fewer intensive care unit beds (Gupta 2020)! Patients admitted to hospitals with fewer than 50 ICU beds versus at least 100 ICU beds had a higher risk of death (OR 3.28; 95% CI, 2.16-4.99).

Reactivations, reinfections

Seasonal coronavirus protective immunity is not long-lasting (Edridge 2020). There are several reports of patients infected with SARS-CoV-2 who became positive again after negative PCR tests (Lan 2020, Xiao 2020, Yuan 2020). These reports have gained much attention, because this could indicate reactivations as well as reinfections. After closer inspection of these reports, however, there is no good evidence for reactivations or reinfections, and other reasons are much more likely. Methodological problems of PCR always have to be considered; the results can considerably fluctuate (Li 2020). Insufficient material collection or storage are just two examples of many problems with PCR. Even if everything is done correctly, it can be expected that a PCR could fluctuate between positive and negative at times when the values are low and the viral load drops at the end of an infection (Wölfel 2020). The largest study to date found a total of 25 (14.5%) of 172 discharged COVID-19 patients who had a positive test at home after two negative PCR results at hospital (Yuan 2020). On average, the time between the last negative and the first positive test was 7.3 (standard deviation 3.9) days. There were no differences to patients who remained negative. This and the short period of time suggest that in these patients, no reactivations are to be expected.

However, in recent months several case reports of true (virologically proven: phylogenetically distinct strains) re-infections have been reported (To 2020, Gupta 2020, Van Elslande 2020). In most cases, the second episode was milder than the first. However, there is at least one case where the second infection was more severe, potentially due to immune enhancement, acquisition of a more pathogenic strain, or perhaps a greater inoculum of infection as the

second exposure was from within household contacts ([Larson 2020](#)). Up to now, however, these are anecdotal case reports.

Animal studies suggest that re-infection is unlikely ([Chandrashekar 2020](#)). Following initial viral clearance and on day 35 following initial viral infection, 9 rhesus macaques were re-challenged with the same doses of virus that were utilized for the primary infection. Very limited viral RNA was observed in BAL on day 1, with no viral RNA detected at subsequent timepoints. These data show that SARS-CoV-2 infection induced protective immunity against re-exposure in nonhuman primates. There is growing evidence for a long-lived and robust T cell immunity that is generated following natural SARS-CoV-2 infection ([Neidleman 2020](#)).

Reactivations as well as rapid new infections would be very unusual, especially for coronaviruses. If a lot of testing is done, you will find a number of such patients who become positive again after repeated negative PCR and clinical convalescence. The phenomenon is likely to be overrated. Most patients get well anyway; moreover, it is unclear whether renewed positivity in PCR is synonymous with infectiousness.

Long-term sequelae

The profound physical impairments associated with critical COVID-19 illness are well known. Many patients with severe COVID-19, especially older patients and those with ARDS, will suffer long-term complications from an intensive care unit stay and from the effects of the virus on multiple body systems such as the lung, heart, blood vessels and the CNS. However, there is growing evidence that even in some younger people with non-severe COVID-19 the illness may continue for weeks, even months. The persistent symptoms in these so-called “long haulers” fluctuate and range from severe fatigue, breathlessness, fast heart rate with minimal exertion, chest pain, pericarditis/myocarditis, hoarseness, skin manifestations and hair loss, acquired dyslexia, headaches, memory loss, relapsing fevers, joint pains, and diarrhea. Symptoms may arise through several mechanisms including direct organ damage and involvement of immune function and the autonomic nervous system. The following key papers address post-acute findings in patients with mild-to-moderate COVID-19.

- In Rome, 143 patients discharged from hospital were assessed after a mean of 60 days after onset of the first COVID-19 symptom. During hospitalization, 73% had evidence of pneumonia but only 15% and 5% received non-invasive or invasive ventilation, respectively. Only 13% were completely free of any COVID-19-related symptom, while 32% had 1-2 symp-

toms and 55% had 3 or more. Many patients reported fatigue (53%), dyspnea (43%), joint pain (27%) and chest pain (28%). A worsened quality of life (QoL) was observed in 44% of patient (Carfi 2020).

- In Paris, persistent symptoms and QoL were assessed in 120/222 patients discharged from a COVID-19 ward unit, at a mean of 111 days after their admission. The most common persistent symptoms were fatigue (55%), dyspnea (42%), loss of memory (34%), concentration and sleep disorders (28% and 31%, respectively) and hair loss (20%). Of note, ward and ICU patients showed no differences with regard to these symptoms. In both groups, EQ-5D (mobility, self-care, pain, anxiety or depression, usual activity) showed a slight difference in pain in the ICU group (Garrigues 2020).
- The only US data to date, including a random sample of adults testing positive at an outpatient visit (Tenforde 2020). Telephone interviews were conducted at a median of 16 (14–21) days after the test date. Among 292 respondents, 94% reported experiencing one or more symptoms at the time of testing; 35% of these reported not having returned to their usual state of health by the date of the interview, increasing from 26% (those aged 18–34 years) to 47% (≥ 50 years).
- Physical fitness before and after infection in 199 young, predominantly male military recruits (Crameri 2020) from Switzerland. Recruits had had a “baseline” fitness test, performed 3 months prior to a large COVID-19 outbreak in the company, including a progressive endurance run. Baseline fitness values were compared with a fitness test at a median of 45 days after SARS-CoV-2 diagnosis. Participants were grouped into convalescent recruits with symptomatic COVID-19 ($n=68$), asymptomatic cases ($n=77$) and a naive group without symptoms or laboratory evidence of SARS-CoV-2 infection ($n=54$). Results: neither of the strength tests differed significantly between the groups. However, there was a significant decrease in VO₂ max among convalescents compared with naive and asymptomatically infected recruits. Around 19% of the COVID-19 convalescents had a decrease of more than 10% in VO₂ max, while none of the naive recruits showed such a decrease.
- The best study to date on cardiac issues, including 100 COVID-19 patients at a mean age of 49 years (Puntmann 2020). The median time between diagnosis and cardiac MRI (CMR) was 71 (64–92) days. Most patients recovered at home ($n=67$), with only minor or moderate ($n=49$) or without any symptoms ($n=18$). Compared with pre-COVID-19 status, 36% reported ongoing shortness of breath and general exhaustion, of whom 25 noted symptoms during less-than-ordinary daily activities, such as household

chores. CMR revealed cardiac involvement in 78% and ongoing myocardial inflammation in 60%, independent of pre-existing conditions, severity of COVID-19 or from the time of diagnosis. The authors concluded that “participants with a relative paucity of pre-existing cardiovascular condition and with mostly home-based recovery had frequent cardiac inflammatory involvement, which was similar to the hospitalized subgroup”.

- A comprehensive CMR examination in 26 competitive athletes, among them 14 asymptomatic and 12 with only mild symptoms. CMR was performed 11-53 days after recommended quarantine ([Rajpal 2020](#)). In total 4/26 (15%) had CMR findings suggestive of myocarditis and 8/26 (31%) exhibited changes suggestive of prior myocardial injury. In 7/12 of patients with pathological findings, CMR had been performed at least three weeks after the positive SARS-CoV-2 test result.
- MRI in 60 COVID-19 patients (47 classified as mild), performed at a mean of 97 days from symptom onset. Compared with 39 age- and sex-matched non-COVID-19 volunteers, recovered COVID-19 patients showed volumetric and micro-structural abnormalities that were detected mainly in the central olfactory cortices and partially in the white matter in the right hemisphere. According to the authors, these abnormalities might cause long-term burden to COVID-19 patients after recovery ([Lu 2020](#)).

Taken together, clinical data is still scarce. However, it is dismissive to solely attribute persisting symptoms after mild or moderate COVID-19 to anxiety or to depression or to label them as anecdotal. “COVID-19 long haulers” are not hypochondriacs. There is an urgent need to quantify long-term complications properly and accurately, including non-hospitalized patients with mild disease, and several prospective studies are underway (Reviews: [Alwan 2020](#), [Greenhalgh 2020](#), [Marshall 2020](#), [Yelin 2020](#)).

Outlook

Over the coming months, serological studies will give a clearer picture of the true number of asymptomatic patients and those with unusual symptoms. More importantly, we have to learn more about risk factors for severe disease, in order to adapt prevention strategies. Older age is the main but not the only risk factor. Recently, a 106-year-old COVID-19 patient recently recovered in the UK. The precise mechanisms of how co-morbidities (and co-medications) may contribute to an increased risk for a severe disease course have to be elucidated. Genetic and immunological studies need to reveal susceptibility and predisposition for both severe and mild courses. Who is really at risk, who is not? Quarantining only the old is too easy.

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8. Treatment

Christian Hoffmann

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Addendum 22 November

On 21 November, the FDA issued an emergency use authorization for **casirivimab** (REGN10933) and **imdevimab** (REGN10987) (see page 343) to be administered together **for the treatment of mild to moderate** COVID-19 in patients of 12 years of age or older (weighing at least 40 kilograms) and who are at high risk for progressing to severe COVID-19 (65 years of age or older or certain chronic medical conditions). Both antibodies are **not authorized** for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19.

Addendum 20 November

WHO issued a conditional recommendation against the use of remdesivir (brand name: Veklury) in hospitalized patients, regardless of disease severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients. Evidence from over 7000 patients across 4 trials suggests no important effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient-important outcomes.

WHO 20201120. **WHO recommends against the use of remdesivir in COVID-19 patients.** WHO 2020, published 20 November. Full-text: <https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients>

Addendum 15 November

On 9 November, the FDA issued an emergency use authorization (EUA) for the investigational monoclonal antibody **bamlanivimab** (see page 344) for the **treatment of mild to moderate** COVID-19 in patients who are 12 years of age and older weighing at least 40 kilograms, and who are at high risk for progressing to severe COVID-19 and/or hospitalization (65 years of age or older, or certain chronic medical conditions). Bamlanivimab is **not authorized** for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19.

* * *

[1 November] Let's face reality: at the beginning of the second pandemic wave, we have some steroids which have been shown to reduce mortality in patients with severe COVID-19 (see *Corticosteroids*, page 349); and then we have a drug, remdesivir (Veklury®), which had a marginal benefit in a company-sponsored trial (Beigel 2020). That's the COVID-19 treatment armamentarium as of October 2020.

Thus, the next 35 pages will discuss many drugs that have shown so far NO effect. So why read this chapter? Because doctors need to know the state-of-the-art – even the 'state-of-the-non-art'. Doctors must know why substances have shown NO effect and why there may still be new, innovative and creative ideas; why the senior physician has been less enthusiastic about tocilizumab over the last few weeks and why the 89-year-old diabetic on Ward 1 still gets remdesivir and famotidine; and why the plasma therapy did not work in the 51 yrs old obese woman who died on Ward 2.

Hopefully, within a few months, this chapter will contain only ten pages. We only need one good drug (or, for that matter, five me-too-drugs). Only one drug that must not even be perfect but could become a game changer in this pandemic (perhaps even more so and even sooner than a vaccine) because good enough to prevent people from becoming seriously ill. One drug to downgrade SARS-CoV-2 to the rank of their stupid seasonal common cold siblings nobody was really interested in during the last decades (except [Christian Drosten](#)).

Research activity is immense. A brief look at [ClinicalTrials.gov](#) illustrates the efforts that are underway: on April 18, the platform listed 657 studies, with 284 recruiting, among them 121 in Phase III randomized clinical trials (RCTs). On October 14, these numbers have increased to 3,598, 1,880 and 230. Unfortunately, many trials exclude those patients most in need: the elderly. A data query of ClinicalTrials.gov on June 8 revealed that 206/674 (31%) COVID-19 interventional trials had an upper age exclusion criterion. The median upper age exclusion was 75 years. Exclusion of older patients dramatically increases the risk of non-representative trial populations compared with their real-world counterparts ([Abi Jaoude 2020](#)).

Different therapeutic approaches are under evaluation: antiviral compounds that inhibit enzyme systems, those inhibiting the entry of SARS-CoV-2 into the cell and, finally, immune therapies, including convalescent plasma and monoclonal antibodies. Some immune modulators may enhance the immune system, others are supposed to reduce the cytokine storm and associated pulmonary damage that is seen in severe cases. In this chapter, we will discuss the most promising agents (those for which at least a bit of clinical data is available). We will not mention all compounds that may work in cell lines

or that have been proposed from virtual screening models. We will also forget some.

On the following pages, the following agents will be discussed:

1. **Inhibitors of viral RNA synthesis**

RdRp Inhibitors	Remdesivir, favipiravir, sofosbuvir
Protease Inhibitors	Lopinavir/r

2. **Other antiviral agents**

Various	APN1, Camostat, Umifenovir Hydroxy/chloroquine
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3. **Antibodies**

Monoclonal antibodies	REGN-CoV-2, other mAbs
Convalescent plasma	

4. **Immune modulators**

Corticosteroids	Dexamethasone, hydrocortisone
Interferons	IFN- α 2b, IFN- β
JAK inhibitors	Baricitinib, ruxolitinib
Cytokine blockers and anticomplement therapies	Anakinra, canakinumab, infliximab, mavrilimumab, tocilizumab, Siltuximab, sarilumab, vilobelimumab

5. **Various treatments** (with unknown or unproven mechanisms of action)

Acalabrutinib, ibrutinib, colchicine, famotidine, G-CSF, iloprost

So please enjoy reading the following pages. Most of the options are ineffective (and in the end, page 360, we will make some brief recommendations).

1. Inhibitors of the viral RNA synthesis

SARS-CoV-2 is a single-stranded RNA betacoronavirus. Potential targets are some non-structural proteins such as protease, RNA-dependent RNA polymerase (RdRp) and helicase, as well as accessory proteins. Coronaviruses do not use reverse transcriptase. There is only a total of 82% genetic identity between SARS-CoV and SARS-CoV-2. However, the strikingly high genetic homology for one of the key enzymes, the RdRp which reaches around 96%, suggests that substances effective for SARS may also be effective for COVID-19.

RdRp inhibitors

Remdesivir (Veklury®)

Remdesivir (RDV) is a nucleotide analog and the prodrug of an adenosine C nucleoside which incorporates into nascent viral RNA chains, resulting in premature termination. It received an “Emergency Use Authorisation” from the FDA in May and a so-called “conditional marketing” authorization from the EMA in July.

In vitro experiments have shown that remdesivir has broad anti-CoV activity by inhibiting RdRp in airway epithelial cell cultures, even at submicromolar concentrations. This RdRp inhibition works in rhesus macaques ([Williamson 2020](#)). The substance is very similar to tenofovir alafenamide, another nucleotide analogue used in HIV therapy. Remdesivir was originally developed by Gilead Sciences for the treatment of the Ebola virus but was subsequently abandoned, after disappointing results in a large randomized clinical trial ([Mulangu 2019](#)). Resistance to remdesivir in SARS was generated in cell culture but was difficult to select and seemingly impaired viral fitness and virulence. However, there is a case report describing the occurrence of a mutation in the RdRp (D484Y) gene following failure of remdesivir ([Martinot 2020](#)). Animal models suggest that a once-daily infusion of 10 mg/kg remdesivir may be sufficient for treatment; pharmacokinetic data for humans are still lacking.

Safety was shown in the Ebola trial. In the Phase III studies on COVID-19, an initial dose of 200 mg was started on day 1, similar to the Ebola studies, followed by 100 mg for another 4-9 days. The key trials are listed here:

- Compassionate Use Program: this was a fragmentary cohort ([Grein 2020](#)) on some patients (only 53/61 patients were analyzed) with varying disease severity. Some improved, some didn't: random noise. We believe, for a number of reasons, that this case series published in the New England Journal of Medicine is a cautionary tale for “science in a hurry”, arousing false expectations. It might have been preferable to postpone the publication ([Hoffmann 2020](#)).
- NCT04257656: This multicentre RCT at ten hospitals in Hubei ([Wang 2020](#)) randomized a total of 237 patients with pneumonia, oxygen saturation of 94% or lower on room air and within 12 days of symptom onset to receive 10 days of single infusions or placebo. Clinical improvement was defined as the number of days to the point of a decline of two levels on a six-point clinical scale (from 1 = discharged to 6 = death). Patients were 65 years old (IQR 56–71), and many were co-treated with lopinavir (28%) and corticosteroids. The trial did not attain the predetermined sample size because

the outbreak was brought under control in China. However, remdesivir was not associated with a difference in time to clinical improvement. Day 28 mortality was 14% versus 13%. Of note, the viral load decreased similarly in both groups. Some patients with remdesivir had dosing prematurely stopped due to adverse events (12% versus 5%, mainly gastrointestinal symptoms and increases of liver enzymes). The positive message from this trial is that time to recovery was “numerically” shorter in the remdesivir group, particularly in those treated within 10 days of symptom onset.

- **SIMPLE 1:** in this randomized, open-label RCT in 397 hospitalized patients with severe COVID-19 and not requiring IMV, clinical improvement at day 14 was 64% with 5 days and 54% with 10 days of remdesivir ([Goldman 2020](#)). After adjustment for (significant) baseline imbalances in disease severity, outcomes were similar. The most common adverse events were nausea (9%), worsening respiratory failure (8%), elevated ALT level (7%), and constipation (7%). Because the trial lacked a placebo control, it was not a test of efficacy for remdesivir. An expansion phase will enroll an additional 5,600 (!) patients around the world.
- The second open-label SIMPLE trial, NCT04292730 (GS-US-540-5774), evaluated the efficacy of two remdesivir regimens compared to standard of care (SOC) in 584 hospitalized patients with moderate COVID-19, with respect to clinical status assessed by a 7-point ordinal scale on day 11. Clinical status distribution was significantly better for those randomized to a 5-day course of remdesivir compared with those randomized to SOC ([Spinner 2020](#)). According to the authors, however, this “difference was of uncertain clinical importance”. The difference for those randomized to a 10-day course (median length of treatment, 6 days) compared with standard of care was not significant. By day 28, 9 patients had died: 2 (1%) and 3 (2%) in the 5-day and 10-day remdesivir groups, and 4 (2%) in the SOC group, respectively. Nausea (10% vs 3%), hypokalemia (6% vs 2%), and headache (5% vs 3%) were more frequent among remdesivir-treated patients, compared with SOC.
- **ACTT (Adaptive COVID-19 Treatment Trial):** The conclusion of the final report for this double-blinded RCT that had randomized 1,062 patients throughout the world, was remarkably short: remdesivir “was superior to placebo in shortening the time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection” ([Beigel 2020](#)). Median recovery time was 10 versus 15 days. On an eight-category ordinal scale, patients who received remdesivir were more likely to improve at day 15. The benefit in recovery persisted when adjustment was made for glucocorticoid use. The Kaplan–Meier estimates of mortality

were 6.7% with remdesivir and 11.9% with placebo by day 15. Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%).

- WHO Solidarity Trial Consortium 2020: Not yet peer reviewed, but important: In SOLIDARITY, 11,266 adults (405 hospitals in 30 countries) were randomized, with 2750 allocated to remdesivir, 954 HCQ, 1411 lopinavir/r, 651 interferon plus lopinavir/r, 1412 only interferon, and 4088 no study drug. Kaplan-Meier 28-day mortality was 12%. No study drug definitely reduced mortality (in unventilated patients or any other subgroup of entry characteristics), initiation of ventilation or hospitalisation duration.

What comes next? Several additional trials are ongoing. Let's wait for the results, before we throw remdesivir into the dump. According to a recent review, remdesivir (5 days) should be prioritized for hospitalized patients requiring low-flow supplemental oxygen as it appears that these patients derive the most benefit (Davis 2020). The data also support some benefit in hospitalized patients breathing ambient air (if there is adequate drug supply). Current data do NOT suggest benefit for those requiring high-flow oxygen or mechanical ventilation (non-invasive or invasive). It has become "clear that treatment with an antiviral drug alone is not likely to be sufficient for all patients" (Beigel 2020).

Of note, some new ideas on remdesivir as an inhalation therapy have been published (Contini 2020). Local instillation or aerosol in the first phase of infection, both in asymptomatic but nasopharyngeal swab positive patients, together with antiseptic-antiviral oral gargles and povidone-iodine eye drops for conjunctiva would attack the virus directly through the receptors to which it binds, significantly decreasing viral replication and the risk of severe COVID-19. Gilead is working on this (knowing that "early intravenous infusions" are not feasible).

Favipiravir

Favipiravir is another broad antiviral RdRp inhibitor that has been approved for influenza in Japan (but was never brought to market) and other countries. Favipiravir is converted into an active form intracellularly and recognized as a substrate by the viral RNA polymerase, acting like a chain terminator and thus inhibiting RNA polymerase activity (Delang 2018). In the absence of scientific data, favipiravir has been granted five-year approval in China under the trade name Favilavir® (in Europe: Avigan®). A loading dose of 2400 mg BID is recommended, followed by a maintenance dose of 1200-1800 mg QD. How-

ever, in 7 patients with severe COVID-19, the favipiravir trough concentration was much lower than that of healthy subjects in a previous clinical trial (Irie 2020). Potential drug-drug interactions (DDIs) have to be considered. As the parent drug undergoes metabolism in the liver mainly by aldehyde oxidase (AO), potent AO inhibitors such as cimetidine, amlodipine, or amitriptyline are expected to cause relevant DDIs (review: Du 2020). Some encouraging preliminary results in 340 COVID-19 patients were reported from Wuhan and Shenzhen (Bryner 2020).

- A first open-label RCT posted on March 26 (Chen 2020) was conducted in 3 hospitals in China, comparing arbidol and favipiravir in 236 patients with pneumonia. Primary outcome was the 7-day clinical recovery rate (recovery of fever, respiratory rate, oxygen saturation and cough relief). In “ordinary” COVID-19 patients (not critical), recovery rates were 56% with arbidol (n = 111) and 71% (n = 98) with favipiravir (p = 0.02), which was well tolerated, except for some elevated serum uric acid levels. However, it remains unclear whether these striking results are credible. In the whole study population, no difference was seen. Many cases were not confirmed by PCR. There were also imbalances between subgroups of “ordinary” patients.
- No effect of viral clearance was found in RCT on 69 patients with asymptomatic to mild COVID-19 who were randomly assigned to early or late favipiravir therapy (same regimen starting day 1 or day 6). Viral clearance occurred within 6 days in 67% and 56%. Of 30 patients who had a fever ($\geq 37.5^{\circ}\text{C}$) on day 1, time to no fever was 2.1 days and 3.2 days (aHR, 1.88; 95% CI 0.81–4.35). During therapy, 84% developed transient hyperuricemia. Neither disease progression nor death occurred in any of the patients in either treatment group during the 28-day study (Doi 2020).
- In the pilot stage of a Phase II/III clinical trial, 60 patients hospitalized with COVID-19 pneumonia were randomized to two different dosing groups or standard of care (Ivashchenko 2020). Favipiravir enabled SARS-CoV-2 viral clearance in 62.5% of patients within 4 days and was safe and well-tolerated. The proportion of patients who achieved negative PCR on day 5 on both dosing regimens was twice as high as in the control group (p < 0.05).

Other RdRp inhibitors: sofosbuvir, galidesivir

Some other RdRp inhibiting compounds have also been discussed. Sofosbuvir is a polymerase inhibitor which is also used as a direct-acting agent in hepatitis C. It is usually well tolerated. Modelling studies have shown that sofos-

buir could also inhibit RdRp by competing with physiological nucleotides for the RdRp active site (Elfiky 2020). Sofosbuvir could be combined with HCV PIs. The first randomized controlled trial in adult patients hospitalized with COVID-19 in Iran to evaluate the efficacy and safety of the two HCV drugs sofosbuvir and daclatasvir in combination with ribavirin (SDR) compared these drugs with standard of care (Abbaspour Kasgari 2020). Though there were trends in favor of the SDR arm for recovery and lower death rates, the trial was too small to make definite conclusions. In addition, there was an imbalance in the baseline characteristics between the arms.

Galidesivir is a nucleoside RNA polymerase inhibitor with broad-spectrum activity *in vitro* against more than 20 RNA viruses in nine different families, including coronaviruses and other viral families. A NIAID-funded, randomized, double-blind, placebo-controlled clinical trial to assess the safety, clinical impact and antiviral effects of galidesivir in patients with COVID-19 is underway. Of note, the drug also works against Zika: in the study presented here, galidesivir dosing in rhesus macaques was safe and offered post-exposure protection against Zika virus infection (Lim 2020).

Protease inhibitors (PIs)

A promising drug target is the viral main protease Mpro, which plays a key role in viral replication and transcription. Some HIV PIs have been extensively studied in COVID-19 patients.

Lopinavir

Lopinavir/r is thought to inhibit the 3-chymotrypsin-like protease of coronaviruses. To achieve appropriate plasma levels, it has to be boosted with another HIV PI called ritonavir (usually indicated by “/r”: lopinavir/r). Due to some uncontrolled trials in SARS and MERS, lopinavir/r was widely used in the first months, despite the lack of any evidence. In an early retrospective study on 280 cases, early initiation of lopinavir/r and/or ribavirin showed some benefits (Wu 2020).

- The first open-label RCT in 199 adults hospitalized with severe COVID-19 did not find any clinical benefit beyond standard of care in patients receiving the drug 10 to 17 days after onset of illness (Cao 2020). There was no discernible effect on viral shedding.
- A Phase II, multicentre, open-label RCT from Hong Kong randomized 127 patients with mild-to-moderate COVID-19 (median 5 days from symptom onset) to receive lopinavir/r only or a triple combination consisting of lopinavir/r, ribavirin and interferon (Hung 2020). The results indicate that

the triple combination can be beneficial when started early (see below, interferon). As there was no lopinavir/r-free control group, this trial does not prove lopinavir/r efficacy.

- After preliminary results were made public on June 29, 2020, we are now facing the full paper on the lopinavir/r arm in the RECOVERY trial: In 1,616 patients admitted to hospital who were randomly allocated to receive lopinavir/r (3,424 patients received usual care), lopinavir/r had no benefit. Overall, 374 (23%) patients allocated to lopinavir/r and 767 (22%) patients allocated to usual care died within 28 days. Results were consistent across all prespecified subgroups. No significant difference in time until discharge alive from hospital (median 11 days in both groups) or the proportion of patients discharged from hospital alive within 28 days was found. Although the lopinavir/r, dexamethasone, and hydroxychloroquine groups have now been stopped, the RECOVERY trial continues to study the effects of azithromycin, tocilizumab, convalescent plasma, and REGN-CoV2.

At least two studies suggested that lopinavir pharmacokinetics in COVID-19 patients may differ from those seen in HIV-infected patients. In both studies, very high concentrations were observed, exceeding those in HIV-infected patients by 2-3 fold ([Schoergenhofer 2020](#), [Gregoire 2020](#)). However, concentrations of protein-unbound lopinavir achieved by current HIV dosing is probably still too low for inhibiting SARS-CoV-2 replication. The EC_{50} for HIV is much lower than for SARS-CoV-2. It remains to be seen whether these levels will be sufficient for (earlier) treatment of mild cases or as post-exposure prophylaxis.

Other PIs

For another HIV PI, darunavir, there is no evidence from either cell experiments or clinical observations that the drug has any prophylactic effect ([De Meyer 2020](#)).

It is hoped that the recently published pharmacokinetic characterization of the crystal structure of the main protease SARS-CoV-2 may lead to the design of optimized protease inhibitors. Virtual drug screening to identify new drug leads that target protease which plays a pivotal role in mediating viral replication and transcription, have already identified several compounds. Six compounds inhibited M(pro) with IC_{50} values ranging from 0.67 to 21.4 μ M, among them two approved drugs, disulfiram and carmofur (a pyrimidine analog used as an antineoplastic agent) drugs ([Jin 2020](#)). Others are in development but still pre-clinical ([Dai 2020](#)).

2. Various antiviral agents

Most coronaviruses attach to cellular receptors via their spike (S) protein. Within a few weeks after the discovery of SARS-CoV-2, several groups elucidated the entry of the virus into the target cell ([Hoffmann 2020](#), [Zhou 2020](#)). Similar to SARS-CoV, SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a key receptor, a surface protein that is found in various organs and on lung AT2 alveolar epithelial cells. The affinity for this ACE2 receptor appears to be higher with SARS-CoV-2 than with other coronaviruses. The hypothesis that ACE inhibitors promote severe COVID-19 courses through increased expression of the ACE2 receptor remains unproven (see chapter *Clinical Presentation*, page 279).

Human recombinant soluble ACE2 (APN01)

HrsACE2 is a therapeutic candidate that neutralizes infection by acting as a decoy. It may act by binding the viral spike protein (thereby neutralizing SARS-CoV-2) and by interfering with the renin-angiotensin system. APN01 has been shown to be safe and well-tolerated in a total of 89 healthy volunteers and patients with pulmonary arterial hypertension (PAH) and ARDS in previously completed Phase I and Phase II clinical trials. It is developed by APEIRON, a privately-held European biotech company based in Vienna, Austria. There is a report of an Austrian case of a 45-year-old woman with severe COVID-19 who was treated with hrsACE2. The virus disappeared rapidly from the serum and the patient became afebrile within hours ([Zoufaly 2020](#)). Several Phase II/III studies of hrsACE2 are ongoing.

Camostat (Foipan®)

In addition to binding to the ACE2 receptor, priming or cleavage of the spike protein is also necessary for viral entry, enabling the fusion of viral and cellular membranes. SARS-CoV-2 uses the cellular protease transmembrane protease serine 2 (TMPRSS2). Compounds inhibiting this protease may therefore inhibit viral entry ([Kawase 2012](#)). The TMPRSS2 inhibitor camostat, approved in Japan for the treatment of chronic pancreatitis (trade name Foipan®), may block the cellular entry of the SARS-CoV-2 virus ([Hoffmann 2020](#)). Clinical data are pending. At least five trials are ongoing, mostly in mild-to-moderate disease.

Umifenovir

Umifenovir (Arbidol®) is a broad-spectrum antiviral drug approved as a membrane fusion inhibitor in Russia and China for the prophylaxis and

treatment of influenza. Chinese guidelines recommend it for COVID-19 - according to a Chinese press release it is able to inhibit the replication of SARS-CoV-2 in low concentrations of 10-30 μM (PR 2020). In a small retrospective and uncontrolled study in mild to moderate COVID-19 cases, 16 patients who were treated with oral umifenovir 200 mg TID and lopinavir/r were compared with 17 patients who had received lopinavir/r as monotherapy for 5–21 days (Deng 2020). At day 7 (day 14) in the combination group, SARS-CoV-2 nasopharyngeal specimens became negative in 75% (94%), compared to 35% (53%) with lopinavir/r monotherapy. Chest CT scans were improving for 69% versus 29%, respectively. Similar results were seen in another retrospective analysis (Zhu 2020). However, a clear explanation for this remarkable benefit was not provided. Another retrospective study on 45 patients from a non-intensive care unit in Jinyintan, China failed to show any clinical benefit (Lian 2020). There is a preliminary report of a randomized study indicating a weaker effect of umifenovir compared to favipiravir (Chen 2020).

Oseltamivir

Oseltamivir (Tamiflu®) is a neuraminidase inhibitor that is approved for the treatment and prophylaxis of influenza in many countries. Like lopinavir, oseltamivir has been widely used for the current outbreak in China (Guan 2020). Initiation immediately after the onset of symptoms may be crucial. Oseltamivir is best indicated for accompanying influenza co-infection, which has been seen as quite common in MERS patients at around 30% (Bleibtreu 2018). There is no valid data for COVID-19. It is more than questionable whether there is a direct effect in influenza-negative patients with COVID-19 pneumonia. SARS-CoV-2 does not require neuramidases to enter target cells.

Hydroxychloroquine (HCQ) and chloroquine (CQ)

HCQ is an anti-inflammatory agent approved for certain autoimmune diseases and for malaria. The story of HCQ in the current pandemic is a warning example of how medicine shouldn't work. Some lab experiments, a mad French doctor, bad uncontrolled studies, many rumors and hopes, reports without any evidence and an enthusiastic tweet that this had “a real chance to be one of the biggest game changers in the history of medicine” - hundreds of thousands people received an ineffective (and potential dangerous) drug. Moreover, many turned away from clinical trials of other therapies that would have required them to give up HCQ treatments. In some countries, the HCQ frenzy prompted serious delays in trial enrolment, muddled efforts to interpret data and endangered clinical research (Ledford 2020). Some countries stockpiled CQ and HCQ, resulting in a shortage of these medications for those that need

them for approved clinical indications. Only a few months later, we are now facing an overwhelming amount of data strongly arguing against any use of both HCQ and CQ. So please, let's forget it. Completely. But let us learn from the bad HCQ story which should never happen again ([Kim 2020](#), [Ledford 2020](#)).

No clinical benefit from Hydroxychloroquine (HCQ)

- In an observational study from New York City ([Geleris 2020](#)) of 1376 hospitalized patients, 811 received HCQ (60% received also azithromycin, A). After adjusting for several confounders, there was no significant association between HCQ use and intubation or death.
- Another retrospective cohort of 1438 patients from 25 hospitals in the New York metropolitan region ([Rosenberg 2020](#)), there were no significant differences in mortality for patients receiving HCQ + Azithromycin (A), HCQ alone, or A alone. Cardiac arrest was significantly more likely seen with HCQ + A (adjusted OR 2.13).
- A randomized, Phase IIb trial in Brazil on severe COVID-19 patients was terminated early ([Borba 2020](#)). By day 13 of enrolment, 6/40 patients (15%) in the low-dose CQ group had died, compared with 16/41 (39%) in the high-dose group. Viral RNA was detected in 78% and 76%, respectively.
- In a study of 251 patients receiving HCQ plus A, extreme new QTc prolongation to > 500 ms, a risk marker for torsades, occurred in 23% ([Chorin 2020](#)).
- In 150 patients with mainly persistent mild to moderate COVID-19, conversion to negative PCR by day 28 was similar between HCQ and SOC ([Tang 2020](#)). Adverse events were recorded more frequently with HCQ (30% vs 9%, mainly diarrhea).
- Symptomatic, non-hospitalized adults with lab-confirmed or probable COVID-19 and high-risk exposure were randomized within 4 days of symptom onset to HCQ or placebo. Among 423 patients, change in symptom severity over 14 days did not differ. At 14 days, 24% receiving HCQ had ongoing symptoms compared with 30% receiving placebo ($p = 0.21$). Adverse events occurred in 43% versus 22% ([Skipper 2020](#)).
- HCQ does not work as a prophylaxis. In 821 asymptomatic participants randomized to receive HCQ or placebo within 4 days of exposure, incidence of confirmed SARS-CoV-2 was 12% with CQ and 14% with placebo. Side effects were more common (40% vs. 17%) ([Boulware 2020](#)).
- No, HCQ does not work as prophylaxis, even in HCW. This double-blind, placebo-controlled RCT included 132 health care workers and was terminated early. There was no significant difference in PCR-confirmed SARS-CoV-2 incidence between HCQ and placebo ([Abella 2020](#)).
- And finally, the RECOVERY Collaborative Group discovered that among 1561 hospitalized patients, those who received HCQ did not have a lower incidence of death at 28 days than the 3155 who received usual care (27% versus 25%).

3. Monoclonal Antibodies and Convalescent Plasma

The development of highly successful monoclonal antibody-based therapies for cancer and immune disorders has created a wealth of expertise and manufacturing capabilities. As long as all other therapies fail or have only modest effects, monoclonal antibodies are the hope for the near future. There is no doubt that antibodies with high and broad neutralizing capacity, many of them directed to the receptor binding domain (RBD) of SARS-CoV-2, are promising candidates for prophylactic and therapeutic treatment. On the other hand, these antibodies will have to go through all phases of clinical trial testing programs, which will take time. Safety and tolerability, in particular, is an important issue. The production of larger quantities is also likely to cause problems. Finally, there is the issue that mAbs are complex and expensive to produce, leaving people from poor countries locked out ([Ledford 2020](#)).

No antibody has been thoroughly tested in humans to date. However, some are very promising. The ‘COVID-19 antibodiesphere’ (Amgen, AstraZeneca, Vir, Regeneron, Lilly, Adagio) is building partnerships. Several mAbs entered clinical trials in the summer of 2020. Trials will include treatment of patients with SARS-CoV-2 infection, with varying degrees of illness, to block disease progression. Given the long half-life of most mAbs (approximately 3 weeks for IgG1), a single infusion should be sufficient.

REGN-COV2

The antibodies given to Trump. REGN10933 binds at the top of the RBD, extensively overlapping the binding site for ACE2, while the epitope for REGN10987 is located on the side of the RBD, away from the REGN10933 epitope, and has little to no overlap with the ACE2 binding site. Proof of principle was shown in a cell model, using vesicular stomatitis virus pseudoparticles expressing the SARS-CoV-2 spike protein. Simultaneous treatment with REGN10933 and REGN10987 precluded the appearance of escape mutants ([Baum 2020](#), [Hansen 2020](#)). Thus, this cocktail called REGN-COV2 did not rapidly select for mutants, presumably because escape would require the unlikely occurrence of simultaneous viral mutation at two distinct genetic sites, so as to ablate binding and neutralization by both antibodies in the cocktail.

- The first clinical data on REGN-COV2 (REGN10933 + REGN10987) were published online on September 29 (not peer reviewed). Regeneron called it “a descriptive analysis on the first ~275 patients”, derived from a broad ongoing clinical development program. Adult, non-hospitalized COVID-19 patients with symptom onset ≤ 7 days from randomization were random-

ized to receive single doses of REGN-COV2 at 2.4 g or 8 g IV or placebo. Before treatment, serology was used to divide patients into positive ($n = 123$) versus negative ($n = 113$). As expected, “viral load” in nasopharyngeal (NP) swabs was higher in seronegative patients (7.18 versus 3.49 \log_{10} copies/mL). Main results showed a modest viral load reduction mainly in seronegative patients and a lack of a numerical dose-response relationship: REGN-COV2 appeared to reduce viral load through day 7 mainly in seronegative patients: the mean NP viral load reduction was -1.98 (high dose) and -1.89 \log_{10} copies/mL (low dose), compared to -1.38 with placebo (difference versus placebo -0.56 for both dosage groups, $p = 0.02$). If all patients were included (including seropositives), the reduction was -1.92 and -1.64 \log_{10} copies/mL, compared to 1.41 with placebo (significance only seen with high dose). Patients with higher baseline viral levels had correspondingly greater reductions in viral load. Median time to symptom alleviation for the overall population (median) was 8, 6 and 9 days for high, low dose and placebo, respectively (seronegative only: 8, 6 and 13). As for medical visits, there was a numerical reduction versus placebo, but with just 12 visits in total there was no way of discerning the relevance. Most non-hospitalized patients recovered well at home. Both doses were well-tolerated. Infusion reactions and severe adverse events were balanced across all groups, no deaths occurred.

Did this save Trump’s life? There is no doubt that larger data are needed in patients with more severe disease. Let’s see what happens. Half a log viral load reduction is not impressive although it may be clinically relevant. If approved, Regeneron will distribute REGN-COV2 in the US and Roche will be responsible for distribution outside the US.

Other mAbs, some key papers:

- Bamlanivimab (LY-CoV555) is a neutralizing IgG1 monoclonal antibody (mAb) directed against the spike protein of SARS-CoV-2. The interim analysis of an ongoing Phase II study in 452 patients with mild to moderate COVID-19 showed some clinical benefit (Chen P 2020). Those who received a single dose bamlanivimab (three different dosages) had fewer hospitalizations (1.6% versus 6.3%) and a lower symptom burden than those who received placebo, with the most pronounced effects observed in high-risk cohorts. However, the viral load at day 11 (the primary outcome) was lower than that in the placebo group only among those who received the 2800-mg dose.
- The first report of a human monoclonal antibody that neutralizes SARS-CoV-2 (Wang 2020). 47D11 binds a conserved epitope on the spike RBD

explaining its ability to cross-neutralize SARS-CoV and SARS-CoV-2, using a mechanism that is independent of receptor-binding inhibition. This antibody could be useful for development of antigen detection tests and serological assays targeting SARS-CoV-2.

- From 60 convalescent patients, 14 potent neutralizing antibodies were identified by high-throughput single B cell RNA-sequencing (Cao 2020). The most potent one, **BD-368-2**, exhibited an IC_{50} of 15 ng/mL against SARS-CoV-2, displaying strong therapeutic efficacy in mice. The epitope overlaps with the ACE2 binding site.
- Several mAbs from ten convalescent COVID-19 patients. The most interesting mAb, named **4A8**, exhibited high neutralization potency but did not bind the RBD (like most other mAbs). Cryo-EM revealed that the epitope of 4A8 seems to be the N terminal domain (NTD) of the S protein (Chi 2020).
- Isolation and characterization of 206 RBD-specific monoclonal antibodies derived from single B cells of eight SARS-CoV-2 infected individuals. Some antibodies showed potent anti-SARS-CoV-2 neutralization activity that correlates with their competitive capacity with ACE2 for RBD binding (Ju 2020).
- **CR3022** tightly binds the RBD and neutralizes SARS-CoV-2 (Huo 2020). The highly conserved, structure-stabilising epitope is inaccessible in the pre-fusion Spike, suggesting that CR3022 binding facilitates conversion to the fusion-incompetent post-fusion state. The mechanism of neutralisation is new and was not seen for coronaviruses.
- **H014** neutralizes SARS-CoV-2 and SARS-CoV pseudoviruses as well as authentic SARS-CoV-2 at nanomolar level by engaging the S receptor binding domain. In the hACE2 mouse model, H014 prevented pulmonary pathology. H014 seems to prevent attachment of SARS-CoV-2 to its host cell receptors (Lv 2020).
- Four human neutralizing monoclonal antibodies were isolated from a convalescent patient. **B38** and **H4** blocked the binding between the virus S protein RBD and the cellular receptor ACE2. A competition assay indicates their different epitopes on the RBD. In a mouse model, both antibodies reduced viral titers in infected lungs. The RBD-B38 complex structure revealed that most residues on the epitope overlap with the RBD-ACE2 binding interface, explaining the blocking effect and neutralizing capacity (Wu 2020).
- Of a total of 178 S1 and RBD binding human monoclonal antibodies from the memory B cells of 11 recently recovered patients, the best one, **414-1**,

showed neutralizing IC_{50} at 1.75 nM (Wan J 2020). Epitope mapping revealed that the antibodies bound to 3 different RBD epitopes, and epitope B antibody 553-15 could substantially enhance neutralizing abilities of most other neutralizing antibodies.

- Isolation and characterization of two ultra-potent SARS-CoV-2 human neutralizing antibodies (S2E12 and S2M11) that were identified among almost 800 screened Abs isolated from 12 COVID-19 patients (Tortorici 2020). Both nAbs protect hamsters against SARS-CoV-2 challenge. Cryo-electron microscopy structures show that S2E12 and S2M11 competitively block ACE2 attachment and that S2M11 also locks the spike in a closed conformation by recognition of a quaternary epitope spanning two adjacent receptor-binding domains. Cocktails including S2M11, S2E12 or the previously identified S309 antibody broadly neutralize a panel of circulating SARS-CoV-2 isolates and activate effector functions.
- Using a high-throughput rapid system for antibody discovery, more than 1000 mAbs were isolated from 3 convalescent donors by memory B cell selection using SARS-CoV-2 S or RBD recombinant proteins. Of note, only a small fraction was neutralizing, highlighting the value of deep mining of responses to access the most potent Abs. RBD-nAbs that directly compete with ACE2 are clearly the most preferred for prophylactic and therapeutic applications, and as reagents to define nAb epitopes for vaccine. With these nAbs, Syrian hamsters were protected from weight loss. However, animals that received higher doses also showed body weight loss, possibly indicating antibody-mediated enhanced disease (Rogers 2020).
- Antibodies from convalescent patients had low levels of somatic hypermutation. Electron microscopy studies illustrate that the SARS-CoV-2 spike protein contains multiple distinct antigenic sites. In total, 19 neutralizing antibodies were identified that target a diverse range of antigenic sites on the S protein, of which two showed picomolar (very strong!) neutralizing activities (Brouwer 2020).
- Isolation of 61 SARS-CoV-2-neutralizing mAbs from 5 hospitalized patients, among which are 19 mAbs that potently neutralized the authentic SARS-CoV-2 *in vitro*, 9 of which exhibited exquisite potency, with 50% virus inhibitory concentrations of 0.7 to 9 ng/mL (Liu 2020).
- Antibody domains and fragments such as VH (heavy chain variable domain, 15 kDa) are attractive antibody formats for candidate therapeutics. They may have better tissue penetration compared to full-sized antibodies. One of those VHs, ab8, in an Fc (human IgG1, crystallizable fragment) fusion format, showed potent neutralization activity and specificity

against SARS-CoV-2 both *in vitro* and in mice and hamsters, possibly enhanced by its relatively small size (Li 2020).

Convalescent plasma (passive immunization)

Human convalescent plasma (CP) could be a rapidly available option for prevention and treatment of COVID-19 disease when there are sufficient numbers of people who have recovered and can donate immunoglobulin-containing serum (Casadevall 2020). Passive immune therapy appears to be relatively safe. However, an unintended consequence of receiving CP may be that recipients won't develop their own immunity, putting them at risk for re-infection. Other issues that have to be addressed in clinical practice (Kupferschmidt 2020) are plasma supply (regulatory considerations; logistical work flow may become a challenge) and rare but relevant risks (transfusion-related acute lung injury, in which transferred antibodies damage pulmonary blood vessels, or transfusion-associated circulatory overload). Fortunately, antibodies that are found in CP are very stable. Pathogen inactivation (using psoralen and UV light) did not impair the stability and neutralizing capacity of SARS-CoV-2-specific antibodies that was also preserved at 100% when the plasma was shock frozen at -30°C after pathogen-inactivation or stored as liquid plasma for up to 9 days (Tonn 2020).

The major caveat of CP is consistency (concentration differs). In plasma from 149 patients collected on average 39 days after the onset of symptoms, neutralizing titers were extremely variable. Most plasmas did not contain high levels of neutralizing activity (Robbani 2020). Pre-screening of CP may be necessary for selecting donors with high levels of neutralizing activity for infusion into patients with COVID-19 (Bradfute 2020). There seems to be a correlation between serum neutralizing capacity and disease severity, suggesting that the collection of CP should be restricted to those with moderate to severe symptoms (Chen 2020). Others have suggested more detailed selection criteria: 28 days after the onset of symptoms with a disease presentation of fever lasting longer than 3 days or a body temperature exceeding 38,5°C. Selection based on these criteria can ensure a high likelihood of achieving sufficiently high titers (Li 2020).

On March 26, the FDA approved the use of plasma from recovered patients to treat people who are critically ill with COVID-19 (Tanne 2020). This was a remarkable decision, and the data is still scarce. Results are at least modest:

- Two small pilot studies with 5 and 10 critically ill patients, showing rapid improvement in their clinical status (Shen 2020, Duan 2020).

- The first RCT was published in June (Li 2020). Unfortunately, the study was terminated prematurely (when the epidemic was under control in China, no more patients could be recruited) and, consequently, underpowered. Of 103 patients who were randomized, clinical improvement (on a 6-point disease severity scale) occurred within 28 days in 52% vs 43%. There was no significant difference in 28-day mortality (16% vs 24%) or time from randomization to discharge. Of note, CP treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87% of the CP group versus 38% (OR, 11.39). Main take-homes: CP is not a silver bullet and anti-viral efficacy does not necessarily lead to better survival.
- The second RCT came from India (Agarwal 2020). This open-label RCT investigated the effectiveness of CP in adults with moderate COVID-19, assigning 235 patients to two doses of 200 mL CP and 229 patients to a control arm. Progression to severe disease or all cause mortality at 28 days occurred in 44 (19%) and 41 (18%). Moreover, CP treatment did not show anti-inflammatory properties and there were no difference between patients with and without neutralizing antibodies at baseline. Main limitation: the antibody titres in CP before transfusion were not measured because validated, reliable commercial tests were not available when the trial started.
- In a retrospective, propensity score-matched case-control study in 39 patients, those who received CP required somewhat less oxygen; preliminary data might suggest a mortality benefit (Liu 2020).
- Compared to 20 matched controls with severe or life-threatening COVID-19 infection, laboratory and respiratory parameters were improved in 20 patients following CP infusion. The 7- and 14-day case fatality rate in CP patients compared favorably (Hegerova 2020). However, this small study was not randomized.
- Don't be too late: Of 6 patients with respiratory failure receiving convalescent plasma at a median of 21 days after first detection of viral shedding, all tested RNA negative by 3 days after infusion. However, 5 eventually died (Zeng 2020).
- Uncontrolled, retrospective data on 1430 patients with severe COVID-19 who received standard treatment only, among them 138 patients who also received ABO-compatible CP (Xia 2020). Despite the higher severity level, only 3 CP patients (2.2%) died, compared to 4.1% patients without CP. However, confounding factors (i.e., biased patient assignments) in this retrospective study could not be ruled out. In addition, complete data on neutralizing antibody titers were unavailable.

4. Immunomodulators

While antiviral drugs are most likely to prevent mild COVID-19 cases from becoming severe, adjuvant strategies will be needed, particularly in severe cases. Coronavirus infections may induce excessive and aberrant, ultimately ineffective host immune responses that are associated with severe lung damage (Channappanavar 2017). Similar to SARS and MERS, some patients with COVID-19 develop acute respiratory distress syndrome (ARDS), often associated with a cytokine storm. This is characterized by increased plasma concentrations of various interleukins, chemokines and inflammatory proteins.

Various host-specific therapies aim to limit the immense damage caused by the dysregulation of pro-inflammatory cytokine and chemokine reactions (Zumla 2020). Immunosuppressants, interleukin-1 blocking agents such as anakinra or JAK-2 inhibitors are also an option (Mehta 2020). These therapies may potentially act synergistically when combined with antivirals. Numerous drugs are discussed, including those for lowering cholesterol, for diabetes, arthritis, epilepsy and cancer, but also antibiotics. They are said to modulate autophagy, promote other immune effector mechanisms and the production of antimicrobial peptides. Other immunomodulatory and other approaches in clinical testing include bevacizumab, brilacidin, cyclosporin, fedratinib, fingolimod, lenadilomide and thalidomide, sildenafil, teicoplanin and many more. However, convincing clinical data is pending for most strategies.

Corticosteroids

Corticosteroids are thus far the only drugs which provide a survival benefit in patients with severe COVID-19. During the first months of the pandemic, according to current WHO guidelines, steroids were controversially discussed and were not recommended outside clinical trials. With a press release on June 16, 2020 reporting the results of the UK-based RECOVERY trial, the treatment of COVID-19 underwent a major change. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation. The RECOVERY results had a huge impact on other RCTs around the world. The therapeutic value of corticosteroids has now been shown in numerous studies:

- RECOVERY: In this open-label trial (comparing a range of treatments), hospitalized patients were randomized to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days (age-adjusted rate ratio, 0.83). The death rate was lower among patients receiving invasive me-

chanical ventilation (29.3% vs. 41.4%) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%) but not among those who were receiving no respiratory support (17.8% vs. 14.0%).

- REMAP-CAP (different countries): In this Bayesian RCT, 384 patients were randomized to fixed-dose ($n = 137$), shock-dependent ($n = 146$), and no ($n = 101$) hydrocortisone. Treatment with a 7-day fixed-dose course or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority, respectively, with regard to the odds of improvement in organ support free days within 21 days. However, due to the premature halt of the trial, no treatment strategy met pre-specified criteria for statistical superiority, precluding definitive conclusions.
- CoDEX (Brazil). A multicenter, open-label RCT in 299 COVID-19 patients (350 planned) with moderate-to-severe ARDS (Tomazini 2020). Twenty mg of dexamethasone intravenously daily for 5 days, 10 mg of dexamethasone daily for 5 days or until ICU discharge, plus standard of care ($n = 151$) or standard of care alone ($n = 148$). Patients randomized to the dexamethasone group had a mean 6.6 ventilator-free days during the first 28 days vs 4.0 ventilator-free days in the standard of care group (difference, 2.26; 95% CI, 0.2-4.38; $p = 0.04$). There was no significant difference in the pre-specified secondary outcomes of all-cause mortality at 28 days, ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, or the 6-point ordinal scale at 15 days.
- CAPE COD: Multicenter double-blinded RCT, in 149 (290 planned) critically-ill patients admitted to the intensive care unit (ICU) for COVID-19-related acute respiratory failure (Dequin 2020). The primary outcome, treatment failure on day 21, occurred in 32 of 76 patients (42.1%) in the hydrocortisone group compared with 37 of 73 (50.7%) in the placebo group ($p = 0.29$).
- A prospective WHO meta-analysis that pooled data from 7 randomized clinical trials that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19. The fixed-effect summary odds ratios for the association with mortality were 0.64 (95% CI, 0.50-0.82; $p < 0.001$) for dexamethasone compared with usual care or placebo, 0.69 (95% CI, 0.43-1.12; $p = 0.13$) for hydrocortisone and 0.91 (95% CI, 0.29-2.87; $p = 0.87$) for methylprednisolone, respectively. There was no suggestion of an increased risk of serious adverse events.
- Another study with 206 patients suggested that the effect of corticosteroids on viral shedding may be in a dose-response manner. High-dose (80

mg/d) but not low-dose corticosteroids (40 mg/d) delayed viral shedding of patients with COVID-19 (Li 2020).

- Treatments for respiratory disease, specifically inhaled corticosteroids (ICSs) do not have a protective effect. In 148,557 persons with COPD and 818,490 persons with asthma who were given relevant respiratory medications in the 4 months before the index date (March 1), people with COPD who were prescribed ICSs were at increased risk of COVID-19-related death compared with those prescribed LABA-LAMA combinations (adjusted HR 1.39) (Schultze 2020). Compared with those prescribed short acting beta agonists only, people with asthma who were prescribed high-dose ICS were at an increased risk of death (1.55, 1.10–2.18)], whereas those given a low or medium dose were not. Sensitivity analyses showed that the apparent harmful association could be explained by relatively small health differences between people prescribed ICS and those not prescribed ICS.

Conclusions: The WHO suggests NOT to use corticosteroids in the treatment of patients with non-severe COVID-19. The WHO recommends systemic corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence). However, the WHO panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously when used for determining which patients should be offered systemic corticosteroids. For example, clinicians must use their judgement to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient suffering from chronic lung disease. Similarly, a saturation above 90–94% on room air may be abnormal if the clinician suspects that this number is on a downward trend.

Interferons

The interferon (IFN) response constitutes the major first line of defense against viruses. This complex host defense strategy can, with accurate understanding of its biology, be translated into safe and effective antiviral therapies. In a recent comprehensive review, the recent progress in our understanding of both type I and type III IFN-mediated innate antiviral responses against human coronaviruses is described (Park 2020).

IFN may work on COVID-19 when given early. Several clinical trials are currently evaluating synthetic interferons given before or soon after infection, in order to tame the virus before it causes serious disease (brief overview: Wadman 2020). *In vitro* observations shed light on antiviral activity of IFN- β 1a against SARS-CoV-2 when administered after the infection of cells, highlight-

ing its possible efficacy in an early therapeutic setting (Clementi 2020). In patients with coronaviruses such as MERS, however, interferon studies were disappointing. Despite impressive antiviral effects in cell cultures (Falzarano 2013), no convincing benefit was shown in clinical studies in combination with ribavirin (Omrani 2014). Nevertheless, inhalation of interferon is still recommended as an option in Chinese COVID-19 treatment guidelines. Of note, in the large SOLIDARITY RCT (paper has not yet been peer-reviewed, see above) there was no effect.

- A Phase II, multicentre, open-label RCT from Hong Kong randomized 127 patients with mild-to-moderate COVID-19 (median 5 days from symptom onset) to receive lopinavir/r only or a triple combination consisting of lopinavir/r, ribavirin and interferon (Hung 2020). This trial indicates that the triple combination can be beneficial when started early. Combination therapy was given only in patients with less than 7 days from symptom onset and consisted of lopinavir/r, ribavirin (400 mg BID), and interferon beta-1b (1-3 doses of 8 Mio IE per week). Combination therapy led to a significantly shorter median time to negative results in nasopharyngeal swab (7 versus 12 days, $p = 0.001$) and other specimens. Clinical improvement was significantly better, with a shorter time to complete alleviation of symptoms and a shorter hospital stay. Of note, all differences were driven by the 76 patients who started treatment less than 7 days after onset of symptoms. In these patients, it seems that interferon made the difference. Up to now, this is the only larger RCT showing a virological response of a specific drug regimen.
- A retrospective multicenter cohort study of 446 COVID-19 patients, taking “advantage of drug stock disparities” between two medical centers in Hubei. Early administration ≤ 5 days after admission of IFN- $\alpha 2b$ was associated with reduced in-hospital mortality in comparison with no admission of IFN- $\alpha 2b$, whereas late administration of IFN- $\alpha 2b$ was associated with increased mortality (Wang 2020).

JAK inhibitors

Several inflammatory cytokines that correlate with adverse clinical outcomes in COVID-19 employ a distinct intracellular signalling pathway mediated by Janus kinases (JAKs). JAK-STAT signalling may be an excellent therapeutic target (Luo 2020).

Baricitinib (Olumiant®) is a JAK inhibitor approved for rheumatoid arthritis. Using virtual screening algorithms, baricitinib was identified as a substance that could inhibit ACE2-mediated endocytosis (Stebbing 2020). Like other JAK

inhibitors such as fedratinib or ruxolitinib, signaling inhibition may also reduce the effects of the increased cytokine levels that are frequently seen in patients with COVID-19. There is some evidence that baricitinib could be the optimal agent in this group (Richardson 2020). Other experts have argued that the drug would be not an ideal option due to the fact that baricitinib causes lymphocytopenia, neutropenia and viral reactivation (Praveen 2020) as well as pancreatitis (Cerdeira-Contreras 2020). There is also a dose-dependent association with arterial and venous thromboembolic events (Jorgensen 2020). It is possible that the pro-thrombotic tendencies could exacerbate a hypercoagulable state, underscoring the importance of restricting the use of baricitinib to clinical trials. Several studies are underway in Italy and the US, among them a huge trial (ACTT-II), comparing baricitinib and remdesivir to remdesivir alone in more than 1,000 patients.

- So far, one observational study provides some evidence for a synergistic effect of baricitinib and corticosteroids (Rodriguez-Garcia 2020). Patients with moderate to severe SARS-CoV-2 pneumonia received lopinavir/r and HCQ plus either corticosteroids (controls, n=50) or corticosteroids and baricitinib (n=62). In the controls, a higher proportion of patients required supplemental oxygen both at discharge (62% vs 26%) and 1 month later (28% vs 13%),

Ruxolitinib (Jakavi®) is a JAK inhibitor manufactured by Incyte. It is used for myelofibrosis, polycythemia vera (PCV) and certain chronic graft versus host diseases in patients following a bone marrow transplant. As many of the elevated cytokines signal through Janus kinase (JAK)1/JAK2, inhibition of these pathways with ruxolitinib has the potential to mitigate the COVID-19-associated cytokine storm and reduce mortality.

- In a retrospective study, 12/14 patients achieved significant reduction of the “COVID-19 Inflammation Score” with sustained clinical improvement in 11/14 patients (La Rosée 2020). Treatment was safe with some signals of efficacy to prevent or overcome multi-organ failure. A Phase II RCT has been initiated (NCT04338958).

Cytokine blockers and anticomplement therapies

The hypothesis that quelling the cytokine storm with anti-inflammatory therapies directed at reducing interleukin-6 (IL-6), IL-1, or even tumour necrosis factor TNF alpha might be beneficial has led to several ongoing trials. It is suggestive that interleukin blocking strategies might improve the hyperinflammatory state seen in severe COVID-19. A recent review on this strategy, however, was less enthusiastic and urged caution (Remy 2020). Past attempts

to block the cytokine storm associated with other microbial infections and with sepsis have not been successful and, in some cases, have worsened outcomes. Moreover, there is concern that suppressing the innate and adaptive immune system to address increased cytokine concentrations, could enable unfettered viral replication, suppress adaptive immunity, and delay recovery processes. There is growing recognition that potent immunosuppressive mechanisms are also prevalent in such patients. Following, we will briefly discuss the evidence on cytokine blockers.

Anakinra (Kineret®) is an FDA-approved treatment for rheumatoid arthritis and neonatal onset multisystem inflammatory disease. It is a recombinant human IL-1 receptor antagonist that prevents the binding of IL-1 and blocks signal transduction. Anakinra is thought to abrogate the dysfunctional immune response in hyperinflammatory COVID-19 and is currently being investigated in almost 20 clinical trials. Some case series have reported on encouraging results.

- A study from Paris, comparing 52 “consecutive” patients treated with anakinra with 44 historical patients. Admission to the ICU for invasive mechanical ventilation or death occurred in 25% of patients in the anakinra group and 73% of patients in the historical group. The treatment effect of anakinra remained significant in the multivariate analysis (Hayem 2020). According to the authors, their study was “not perfect from a statistical point of view...”
- A retrospective cohort study at the San Raffaele Hospital in Milan, Italy, including 29 patients with moderate-to-severe ARDS and hyperinflammation (serum C reactive protein, CRP \geq 100 mg/L) who were managed with non-invasive ventilation and HCQ and lopinavir/r (Cavalli 2020). At 21 days, treatment with high-dose anakinra was associated with reductions in CRP and progressive improvements in respiratory function in 21/29 (72%) patients.
- Another small case series of critically ill patients with secondary hemophagocytic lymphohistocytosis (sHLH) characterized by pancytopenia, hypercoagulation, acute kidney injury and hepatobiliary dysfunction. At the end of treatment, ICU patients had less need for vasopressors and significantly improved respiratory function. Although 3/8 patients died, the mortality was lower than historical series of patients with sHLH in sepsis (Dimopoulos 2020).

Canakinumab (Illaris®) is human monoclonal antibody against IL-1 β , approved for the treatment of juvenile rheumatoid arthritis and other chronic autoinflammatory syndromes. In a pilot trial, 10 patients with hyperinflam-

mation (defined as CRP ≥ 50 mg/L) and respiratory failure showed a rapid improvement in serum inflammatory biomarkers and an improvement in oxygenation (Ucciferri 2020).

Infliximab (Remicade®) is a chimeric monoclonal anti-TNF antibody, approved to treat a number of autoimmune diseases, including Crohn's disease, ulcerative colitis, rheumatoid arthritis and psoriasis. As a major component of deteriorating lung function in patients with COVID-19 is capillary leak, a result of inflammation driven by key inflammatory cytokines such as TNF, making TNF-blocking agents an attractive strategy (Robinson 2020). Administration of anti-TNF to patients for treatment of autoimmune disease leads to reductions in all of these key inflammatory cytokines. A small case series of seven patients who were treated with a single infusion of IFX (5 mg/kg body weight) has been reported (Stallmach 2020).

Mavrilimumab is an anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor- α monoclonal antibody. GM-CSF is an immunoregulatory cytokine with a pivotal role in initiation and perpetuation of inflammatory diseases (Mehta 2020). In small uncontrolled pilot trial on 13 patients, mavrilimumab treatment was associated with improved clinical outcomes compared with standard of care in non-mechanically ventilated patients with severe COVID-19 pneumonia and systemic hyperinflammation. Treatment was well tolerated (De Luca 2020).

Tocilizumab (TCZ, RoActemra® or Actemra®) is a monoclonal antibody that targets the interleukin-6 receptor. It is used for rheumatic arthritis and has a good safety profile. The initial dose should be 4-8 mg/kg, with the recommended dosage being 400 mg (infusion over more than 1 hour). Several RCTs are underway. Of note, the current level of evidence supporting the use of TCZ is weak.

- In a retrospective cohort of COVID-19 patients who required ICU support, deaths occurred in 102/210 (49%) patients with TCZ and in 256/420 (61%) who did not receive TCZ (Biran 2020). After propensity matching, an association was noted between receiving TCZ and decreased mortality (HR 0.64, 95% CI 0.47–0.87).
- In another cohort from Italy (Guaraldi 2020), fewer deaths occurred in 179 patients treated with TCZ compared to 365 patients without TCZ (7% vs 20%). After adjustment for sex, age, duration of symptoms, and SOFA score, TCZ treatment was associated with a reduced risk of ventilation or death (adjusted HR 0.61, 95% CI 0.40–0.92).
- A large multicenter cohort included 3924 critically ill patients admitted to ICU at 68 hospitals across the US (Gupta 2020). The risk of in-hospital

death was lower with TCZ (29% versus 41%). However, TCZ patients were younger and had fewer comorbidities. According to the authors, the findings “may be susceptible to unmeasured confounding, and further research from randomized clinical trials is needed”.

- On July 29, Hoffmann-La Roche announced disappointing results from its much-anticipated Phase III COVACTA trial. TCZ did not improve patient mortality, although patients spent roughly a week less in hospital compared with those given placebo (the full results of the trial have not yet been published). However, it may be too early to quit this strategy ([Furrow 2020](#)). Cautious interpretation of COVACTA is needed, in view of the study’s broad patient selection criteria and other study design factors.
- A double-blind, placebo-controlled RCT in 243 moderately ill hospitalized patients, TCZ was not effective for preventing intubation or death ([Stone 2020](#)).
- An open label RCT in 126 patients hospitalized with COVID-19 pneumonia, the rate of the primary clinical endpoint (clinical worsening) was not significantly different between the control group and the TCZ group ([Salvarani 2020](#)). The proportion of patients discharged within 14 and 30 days was the same. According to the authors, however, their results “do not allow ruling out the possible role of tocilizumab in reducing the risk of death or intubation in patients presenting with more advanced disease”.

Siltuximab (Sylvant[®]) is another anti-IL-6-blocking agent. However, this chimeric monoclonal antibody targets interleukin-6 directly and not the receptor. Siltuximab has been approved for idiopathic multicentric Castleman’s disease (iMCD). In these patients it is well tolerated. First results of a pilot trial in Italy (“SISCO trial”) have shown encouraging results. According to interim interim data, presented on April 2 from the first 21 patients treated with siltuximab and followed for up to seven days, one-third (33%) of patients experienced a clinical improvement with a reduced need for oxygen support and 43% of patients saw their condition stabilise, indicated by no clinically relevant changes ([McKee 2020](#)).

Sarilumab (Kevzara[®]) is another recombinant human IL-6 receptor antagonist. An open-label study of sarilumab in severe COVID-19 pneumonia with hyperinflammation. Sarilumab 400 mg was administered intravenously in addition to standard of care to 28 patients and results were compared with 28 contemporary matched patients treated with standard of care alone. At day 28, 61% of patients treated with sarilumab experienced clinical improvement and 7% died. These findings were not significantly different from the comparison group. However, sarilumab was associated with faster recovery in a sub-

set of patients showing minor lung consolidation at baseline (Della-Torre 2020).

Vilobelimab is an anaphylatoxin and complement protein C5a blocking monoclonal antibody. In an open-label, randomized Phase II trial (part of the PANAMO trial), 30 patients with severe COVID-19 were randomly assigned 1:1 to receive vilobelimab (up to seven doses of 800 mg intravenously) or best supportive care only (control group). At day 5 after randomization, the primary endpoint of mean relative change in the ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air ($\text{PaO}_2/\text{FiO}_2$) was not significantly different between groups. Kaplan-Meier estimates of mortality by 28 days were 13% (95% CI 0–31) for the vilobelimab group and 27% (4–49) for the control group. The frequency of serious adverse events was similar between groups and no deaths were considered related to treatment assignment. According to the authors, the secondary outcome results support the investigation of vilobelimab in a Phase III trial using 28-day mortality as the primary endpoint. Pharmacokinetic and pharmacodynamic data, including C5a, have not yet been published (Campbell 2020). Investigators using the other C5 complement pathway inhibitors eculizumab and ravulizumab have significantly increased their dose and dosing frequency in the acute setting of COVID-19 compared with the doses approved for use in atypical hemolytic uremic syndrome.

Other treatments for COVID-19 (with unknown or unproven mechanisms of action)

Acalabrutinib and ibrutinib

Acalabrutinib and ibrutinib are bruton tyrosine kinase inhibitors, used for CLL and lymphoma treatment. *Ex vivo* analysis revealed significantly elevated BTK activity (BTK regulates macrophage signalling and activation), as evidenced by autophosphorylation, and increased IL-6 production in blood monocytes from patients with severe COVID-19 compared with blood monocytes from healthy volunteers. In a pilot study, 19 patients with severe COVID-19 received the BTK inhibitor acalabrutinib (Roschewski 2020). Within 10–14 days, oxygenation improved “in a majority of patients”, often within 1–3 days, and inflammation markers and lymphopenia normalized quickly in most patients. At the end of acalabrutinib treatment, 8/11 (72.7%) patients in the supplemental oxygen cohort had been discharged on room air. These results suggest that targeting excessive host inflammation with a BTK inhibitor can be a therapeutic strategy. A confirmatory RCT is underway. Some reports

have speculated about a protective effect of ibrutinib, another BTK inhibitor (Thibaud 2020).

Colchicine

Colchicine is one of the oldest known drugs which has been used for over 2000 years as a remedy for acute gout flares. Given its anti-inflammatory and anti-viral properties, it is also being tested in COVID-19 patients. In a prospective, open-label RCT from Greece, 105 hospitalized patients were randomized to either standard of care (SOC) or colchicine plus SOC (Deftereos 2020). Participants who received colchicine had statistically “significantly improved time to clinical deterioration”. However, there were no significant differences in biomarkers and the observed difference was based on a narrow margin of clinical significance; according to the authors their observations “should be considered hypothesis generating” and “be interpreted with caution”. In a retrospective cohort there was some evidence on clinical benefit (Brunetti 2020).

Famotidine

Famotidine is a histamine-2 receptor antagonist that suppresses gastric acid production. It has an excellent safety profile. Initially it was thought to inhibit the 3-chymotrypsin-like protease (3CLpro), but it seems to act rather as an immune modulator, via its antagonism or inverse-agonism of histamine signaling. While results of the randomized clinical trial on the benefits of intravenous famotidine in treating COVID-19 (NCT04370262) are eagerly awaited, we can only speculate on the potential mechanisms of action of this drug (Singh 2020).

- In a retrospective study on 1620 patients, 84 (5.1%) received different doses of famotidine within 24 hours of hospital admission (Freedberg 2020). After adjusting for baseline patient characteristics, use of famotidine remained independently associated with risk for death or intubation (adjusted hazard ratio 0.42, 95% CI 0.21-0.85) and this remained unchanged after careful propensity score matching to further balance the co-variables. Of note, there was no protective effect of PPIs. Plasma ferritin values during hospitalization were lower with famotidine, indicating that the drug blocks viral replication and reduces the cytokine storm.
- A second propensity-matched observational study included 878 consecutive COVID-19-positive patients admitted to Hartford hospital, a tertiary care hospital in Connecticut, USA (Mather 2020). In total, 83 (9.5%) patients received famotidine. These patients were somewhat younger (63.5

vs 67.5 years) but did not differ with respect to baseline demographics or pre-existing comorbidities. Use of famotidine was associated with a decreased risk of in-hospital mortality (odds ratio 0.37, 95% CI 0.16-0.86) and combined death or intubation (odds ratio 0.47, 95% CI 0.23-0.96). Patients receiving famotidine displayed lower levels of serum markers for severe disease including CRP, procalcitonin and ferritin levels. Logistic regression analysis demonstrated that famotidine was an independent predictor of both lower mortality and combined death/intubation.

G-CSF

G-CSF may be helpful in some patients ([Cheng 2020](#)). In an open-label trial at 3 Chinese centers, 200 patients with lymphopenia and no comorbidities were randomized to standard of care or to 3 doses of recombinant human G-CSF (5 µg/kg, subcutaneously at days 0-2). Time to clinical improvement was similar between groups. However, the proportion of patients progressing to ARDS, sepsis, or septic shock was lower in the rhG-CSF group (2% vs 15%). Mortality was also lower (2% vs 10%).

Iloprost

Iloprost is a prostacyclin receptor agonist that promotes vasodilation of circulatory beds with minimal impact on hemodynamic parameters. It is licensed for the treatment of pulmonary arterial hypertension and is widely used for the management of peripheral vascular disease and digital vasculopathy, including digital ulcers and critical digital ischemia in systemic sclerosis. There is a case series of three morbidly obese patients with severe COVID-19 and systemic microvasculopathy who obviously benefitted from its use ([Moezinia 2020](#)).

Other treatments with no effects

Azithromycin

Azithromycin as a macrolide antibiotic has probably no effect against SARS-CoV-2 (see the many studies above, testing it in combination with HCQ). In a large RCT conducted at 57 centers in Brazil, 214 patients who needed oxygen supplementation of more than 4 L/min flow, high-flow nasal cannula, or mechanical ventilation (non-invasive or invasive) were assigned to the azithromycin group and 183 to the control group. Azithromycin had no effect ([Furtado 2020](#)).

Leflunomide

Leflunomide (Arava[®]) is an approved antagonist of dihydroorotate dehydrogenase, has some antiviral and anti-inflammatory effects and has been widely used to treat patients with autoimmune diseases. In a small RCT from Wuhan on 50 COVID-19 patients with prolonged PCR positivity, no benefit in terms of the duration of viral shedding was observed with the combined treatment of leflunomide and IFN α -2a vs IFN α -2a alone ([Wang 2020](#)).

N-acetylcysteine

N-acetylcysteine had no effect, even at high-doses ([De Alencar 2020](#)). In an RCT from Brazil of 135 patients with severe COVID-19, 16 patients (24%) in the placebo group were submitted to endotracheal intubation and mechanical ventilation, compared to 14 patients (21%) in the NAC group ($p = 0.675$). No difference was observed on secondary endpoints.

Outlook and Recommendations

It is hoped that at least some of the options given in this overview will show positive results over time. It is also important, though, that despite the immense pressure, the basic principles of drug development and research including repurposing are not abandoned. Time is needed.

The aim of the COVID Reference textbook is to scan the literature, not to write guidelines. However, after reviewing the studies published until October 15 presented above, we would recommend reviewing the following treatment options, considering the severity of the disease:

Outpatient, mild to moderate (no risk factors)

- Do NOTHING, except downtalking the patient. And make sure that he or she (and their households) stays home

Outpatient, mild to moderate (with risk factors)

- Do NOT use dexamethasone (could be harmful) or remdesivir (daily infusions not feasible)
- Do NOT use hydroxychloroquine, chloroquine, tocilizumab, convalescent plasma or lopinavir (not efficient, plus side effects)
- Famotidine: why not? Potential harm seems to be limited
- Consider REGN-COV2 (if you are the personal doctor of a famous person)

- Interferon may work, if given early (optimal usage and administration is unclear)

Hospital, severe

- Use dexamethasone (only a few days)
- Use remdesivir (5 days) as soon as possible (no benefit in those requiring high-flow oxygen or mechanical ventilation)
- Consider tocilizumab or other cytokine blocking agents, if available

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9. Severe COVID-19

Markus Unnewehr

Peter Rupp

Matthias Richl

Definition and classification

In a small percentage of patients, COVID-19 will take a severe course. As seen in the chapter *Clinical Presentation* (page 297), there was no broadly accepted clinical definition for severe COVID-19 at the beginning of the pandemic. According to a brief and practical definition by IDSA (Infectious Diseases Society of America), severe COVID is defined by “SpO₂ ≤94% on room air, including patients on supplemental oxygen” and critical COVID is “mechanical ventilation and ECMO” (Bhimraj). In this chapter, all symptomatic cases not mild or moderate (i.e. severe and critical) are termed as severe.

Features, course and outcome

The course of the disease as well as the outcome have changed during the pandemic. Most studies refer to the early pandemic phase and cover severely affected regions and countries. The results vary greatly from country to country and depend on the timing as well. The first data from China revealed shocking numbers at a moment when local epidemics were taking off in Europe (Wu 2020). The spectrum of disease was classified as mild in 81% of cases. In total, 14% were classified as severe, and 5% were critical cases. The case-fatality rate was 14.8% in patients aged ≥ 80 years and 8.0% in patients aged 70-79 years. In a large single-center case study on 344 severe and critically ill patients admitted to Tongji hospital in **China** from January 25 through February 25, 2020, 133 (38.7%) patients died at a median of 15 days (Wang 2020). Besides older age, hypertension and COPD were more common in non-survivors but not diabetes. No difference was seen between patients with or without ACE inhibitors.

An observational study on 10,021 adult patients with a confirmed COVID-19 diagnosis, who were admitted to 920 hospitals in **Germany** between 26 February and 19 April 2020 revealed a huge death toll. The median age was 72 years and 1,727 patients (17%) needed mechanical ventilation. Patients on mechanical ventilation had more co-morbidities than patients without mechanical ventilation. Morbidity and mortality were particularly high in older patients, with a considerably lower mortality among patients younger than 60 years

(Karagiannidis 2020). Mortality was 52% (906/1,727) in patients being mechanically ventilated, with lower rates reaching 63% of patients aged 70–79 years and 72% of patients aged 80 years and older (Table 1). In-hospital mortality in ventilated patients who were also treated with dialysis was particularly high at 73% (342 of 469), and 71% (84 of 119) of patients on extracorporeal membrane oxygenation (ECMO) died.

Table 1. In house mortality in patients with/without ventilation, percentage of absolute numbers

	Without ventilation	With ventilation (all types)
18-59 years	0.7% (n = 2474)	27.7% (n = 422)
60-69 years	5.4% (n = 1239)	45.5% (n = 382)
70-79 years	14.6% (n = 1623)	62.6% (n = 535)
≥ 80 years	33.8% (n = 2958)	72.2% (n = 388)

High mortality rates were also seen in other countries. During the early phase of the pandemic, chances of surviving an ICU stay in **Lombardia, Italy**, were only 50% (Grasselli 2020). In a large cohort study of 3988 critically ill patients, most required invasive mechanical ventilation, and mortality rate was high. In the subgroup of the first 1715 patients, 915 patients died in the hospital for an overall hospital mortality of 53.4%.

The mortality in patients requiring mechanical ventilation was equally large in the **New York City** Area at the beginning of the pandemic (Richardson 2020). A case series from New York included 5700 COVID-19 patients admitted to 12 hospitals between March 1 and April 4, 2020. Median age was 63 years (IQR 52-75), the most common co-morbidities were hypertension (57%), obesity (42%), and diabetes (34%). At triage, 31% of patients were febrile, 17% had a respiratory rate greater than 24 breaths/minute, and 28% received supplemental oxygen. Of 2634 patients with an available outcome, 14% (median age 68 years, IQR 56-78, 33% female) were treated in ICU, 12% received invasive mechanical ventilation and 21% died. Mortality for those requiring mechanical ventilation was 88.1%.

In another study in **New York City** among 1,150 adults who were admitted to two NYC hospitals with COVID-19 in March, 257 (22%) were critically ill (Cummings 2020). The median age of patients was 62 years (IQR 51-72), 67% were men and 82% patients had at least one chronic illness. As of the end of April, 101 (39%) patients had died and 94 (37%) remained hospitalized. 203 (79%) patients received invasive mechanical ventilation for a median of 18 days, 66% received vasopressors and 31% received renal replacement therapy.

In a multivariate Cox model, older age, chronic cardiac disease (adjusted HR 1.76) and chronic pulmonary disease (2.94) were independently associated with in-hospital mortality. This was also seen for higher concentrations of interleukin-6 and D-dimer, highlighting the role of systemic inflammation and endothelial-vascular damage in the development of organ dysfunction.

COVID-19 characteristics may vary considerably by location. In a **United States** cohort of 2215 adults who were admitted to ICUs at 65 sites, 784 (35.4%) died within 28 days (Gupta 2020). However, mortality showed an extremely wide variation among hospitals, ranging from 6.6% to 80.8%. Factors associated with death included older age, male sex, obesity, coronary artery disease, cancer, acute organ dysfunction, and, importantly, admission to a hospital with fewer intensive care unit beds. Of note, patients admitted to hospitals with fewer than 50 ICU beds versus at least 100 ICU beds had a higher risk of death (OR 3.28; 95% CI, 2.16-4.99).

Another large prospective observational study in the **United Kingdom** presented clinical data from 20,133 patients, admitted to (or diagnosed in) 208 acute care hospitals in the UK until April 19 (Docherty 2020). Median age was 73 years (interquartile range 58-82) and 60% were men. Co-morbidities were common, namely chronic cardiac disease (31%), diabetes (21%) and non-asthmatic chronic pulmonary disease (18%). Overall, 41% of patients were discharged alive, 26% died, and 34% continued to receive care. 17% required admission to high dependency or intensive care units; of these, 28% were discharged alive, 32% died, and 41% continued to receive care. Of those receiving mechanical ventilation, 17% were discharged alive, 37% died, and 46% remained in hospital. Increasing age, male sex, and co-morbidities including chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease and obesity were associated with higher mortality in hospital.

Spotlight: The situation in a German COVID-19 hospital

The *Klinik Mühldorf am Inn* Hospital was designated as a COVID-19 clinic on March 16, 2020, in order to keep other facilities free for emergencies and elective care. From that day, a total of 276 SARS-CoV-2 positive and 730 suspected cases were treated there. The largest number of symptomatic patients was admitted at the end of March, and the highest number of simultaneously treated SARS-CoV-2 positive patients was 100 patients on April 6, 2020. In total, 18.5% of these in-patients received intensive care during their hospital stay. The peak of intensive care patients was highest on April 10, 2020 with 17 patients. Due to timely preparation, no triage decisions about withholding ventilation treatments had to be made. All COVID-19 patients who had to be

treated in the hospital until July 15th, 2020, and who were in need of mechanical ventilation received it. A total of 51 COVID-19 patients required intensive care treatment (18.5% of all COVID-19 in-patients) and 37 patients (13.4%) were ventilated during their intensive care stay. Seven patients were directly intubated and invasively ventilated without a non-invasive ventilation (NIV) attempt after administration of oxygen through a nasal cannula or mask alone. In total, 9/37 patients did not wish to be intubated. In 16 patients, a prone positioning was carried out, including one patient under NIV.

Management and mechanical ventilation

The cardinal COVID-19 symptom leading to intensive care admission is hypoxemic respiratory failure with tachypnea ($> 30/\text{min}$). Initially, in order to protect staff from aerosols as much as possible, intubation and invasive mechanical ventilation was preferred over non-invasive ventilation (NIV) and nasal high-flow (HFNC).

Likewise, due to lack of knowledge and experience, recommendations on how to deal with these patients were not homogeneous, and ARDS ventilation was the preferred technique (Griffiths 2019). According to the ARDS recommendations, patients should be ventilated with a tidal volume (VT) of $< 6\text{ml/kg}$ standardized body weight, a peak pressure of $< 30\text{ cmH}_2\text{O}$ and a PEEP based on the ARDS network table.

In one study, these ventilator settings were used except for the lower PEEP/higher FiO_2 table. The driving pressure should not exceed 15 mbar. In addition, prone positioning was recommended in case of a $\text{P}_a\text{O}_2/\text{F}_i\text{O}_2 < 150$ for more than 16 hours (Ziehr 2020).

Quickly it became obvious that acute respiratory distress syndrome (ARDS) in COVID-19 is not the same as ARDS. COVID-19 in patients with ARDS – CARDs – appears to include an important vascular insult that potentially mandates a different treatment approach than customarily used for ARDS. It may be helpful to categorize patients as having either type L or H phenotype and accept that different ventilatory approaches are needed, depending on the underlying physiology (Marini 2020). In type L (low lung elastance, high compliance, low response to PEEP), infiltrates are often limited in extent and initially characterized by a ground-glass pattern on CT that signifies interstitial rather than alveolar edema. Many patients do not appear overtly dyspneic and may stabilize at this stage without deterioration. Others may transit to a clinical picture more characteristic of typical ARDS: Type H shows extensive CT consolidations, high elastance (low compliance) and high PEEP response. Clearly, types L and H are the conceptual extremes of a spectrum that includes intermediate stages.

Factors and characteristics to develop one type over the other have been identified: severity of the initial infection, the patient's immune response, the patient's physical fitness and comorbidities, the response of the hypoxemia to the ventilation, and the time between first symptoms and hospital admission (Gattinoni 2020). L type patients remain stable before improvement or deterioration. In the latter case the patients develop H type pneumonia (Pfeifer 2020). According to this theory, a ventilation strategy starting with respiratory support with high flow oxygen has been recommended (Gattinoni 2020).

To adequately assess oxygenation, the oxygen content (CaO_2) in the blood is helpful, as it describes the actual oxygen supply (DO_2) better than the oxygen partial pressure (pO_2), particularly when combined with the cardiac output (CO):

$$\text{DO}_2 = \text{CaO}_2 \times \text{CO} \quad \text{and} \quad \text{CaO}_2 = \text{Hb} \times \text{SaO}_2 \times 1.4$$

With a CaO_2 limit of 10 g/100 ml blood, and an appropriate cardiac output, i.e., absence of cardiac failure, a lower O_2 saturation (hypoxemia) can be tolerated in the blood before a critical oxygen shortage in the tissue (hypoxia) develops.

Therefore, rather than strictly focusing on pO_2 values as represented by the oxygenation index $\text{P}_{\text{aO}_2}/\text{F}_{\text{iO}_2}$ of < 150 , it is more reasonable to consider the overall clinical picture while setting individual target values before intubation. Attempting high-flow oxygen and non-invasive ventilation in patients with type L pneumonia is recommended. Intubation should only be performed if there is significant clinical deterioration (Lyons 2020, Pfeifer 2020).

Special situations in severe COVID-19

Prone positioning

Prone position (PP) has become a therapeutic option, even in awake, non-intubated patients, during spontaneous and assisted breathing (Telias 2020). In one study, among 50 patients, the median SpO_2 at triage was 80%. After supplemental oxygen was given to patients on room air it was 84%. After 5 minutes of proning was added, SpO_2 improved to 94% (Caputo 2020). Whether PP prevents intubation is not known yet.

In a prospective before-after study in Aix-en-Provence, France among 24 awake, non-intubated, spontaneously breathing patients with COVID-19 and hypoxemic acute respiratory failure requiring oxygen supplementation, the effect of PP was only moderate. 63% were able to tolerate PP for more than 3 hours. Oxygenation increased in only 25% and was not sustained in half of

those after resupination. However, prone sessions were short, partly because of limited patient tolerance (Elharrar 2020).

In a small single-center cohort study, use of the prone position for 25 awake, spontaneously breathing patients with COVID-19 was associated with improved oxygenation. In addition, patients with an SpO₂ of 95% or greater after 1 hour of the prone position had a lower rate of intubation. Unfortunately, there was no control group and the sample size was very small. Ongoing clinical trials of prone positioning in non-mechanically ventilated patients (NCT04383613, NCT04359797) will hopefully help clarify the role of this simple, low-cost approach for patients with acute hypoxemic respiratory failure (Thompson 2020).

Extracorporeal Membrane Oxygenation (ECMO)

Since the beginning of the pandemic, extracorporeal lung replacement procedures such as ECMO have been recommended with caution and only in selected patients with severe and persistent hypoxemia ($P_{aO_2}/F_{iO_2} < 80$), with minor comorbidities and with full usage of all other measures, such as relaxation and recruiting maneuvers (Smereka 2020).

In a single center narrative study regarding ECMO, support for 27 patients with COVID-19 was described (Kon 2020). At the time of the paper submission, survival was 96.3% (one death) in over 350 days of total ECMO support. Thirteen patients (48.1%) remained on ECMO support, while 13 patients (48.1%) were successfully decannulated. Seven patients (25.9%) were discharged from the hospital while six patients (22.2%) remained in the hospital, of which four were on (unmodified) room air. The authors conclude that the judicious use of ECMO support may be clinically beneficial.

Tracheostomy

During the pandemic, an old problem in a new situation arose: When to perform tracheostomy (and how) in COVID-19 patients? In a review of the current evidence and misconceptions that predispose to uncontrolled variation in tracheostomy among COVID-19 patients, the authors conclude that decisions on tracheostomy must be personalized; that some patients may be awake but cannot yet be extubated (favoring tracheostomy); while others may have immediate, severe hypoxemia when lying supine or with any period of apnea (favoring deferral) (Tay 2020, Schultz 2020). Meanwhile, detailed consensus guidance has been published, including on important issues such as timing of tracheostomy (delayed until at least day 10 of mechanical ventilation and considered only when patients are showing signs of clinical im-

provement), optimal setting (hierarchical approach to operative location, enhanced PPE), optimal procedure and management after tracheostomy (McGrath 2020).

Lung Transplantation

As in other terminal lung diseases, lung transplantation (LTX) can be a potential therapeutic option. Of course, the indication needs to be considered especially careful. In an editorial published in August 2020, the authors list ten considerations that they believe should be carefully weighed when assessing a patient with COVID-19-associated ARDS regarding potential candidacy for lung transplantation (< 65 years, only single-organ dysfunction, sufficient time for lung recovery, radiological evidence of irreversible lung disease, such as severe bullous destruction or established fibrosis, etc) (Cypel 2020).

Up to now, only case reports have been published. After 52 days of critical COVID-19, ECMO and several complications, a comprehensive interdisciplinary discussion on the direction of treatment resulted in a consensus that the lungs of the otherwise healthy 44-year-old woman from Klagenfurt, Austria had no potential for recovery. On day 58, a suitable donor organ became available, and a sequential bilateral lung transplant was performed. At day 144, the patient remained well. Despite the success of this case, the authors emphasize that lung transplantation is an option for only a small proportion of patients (Lang 2020).

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10. Comorbidities

Christian Hoffmann

Hundreds of articles have been published over the last six months, making well-meaning attempts to determine whether patients with different comorbidities are more susceptible for SARS-CoV-2 infection or at higher risk for severe disease. This deluge of scientific publications has resulted in worldwide uncertainty. For a number of reasons, many studies must be interpreted with extreme caution.

First, in many articles, the number of patients with specific comorbidities is low. Small sample sizes preclude accurate comparison of COVID-19 risk between these patients and the general population. They may also overestimate mortality, especially if the observations were made in-hospital (reporting bias). Moreover, the clinical manifestation and the relevance of a condition may be heterogeneous. Is the hypertension treated or untreated? What is the stage of the COPD, only mild or very severe with low blood oxygen levels? Is the “cancer” cured, untreated or actively being treated? Are we talking about a seminoma cured by surgical orchiectomy years ago or about palliative care for pancreatic cancer? What is a “former” smoker: someone who decided to quit 20 years ago after a few months puffing during adolescence or someone with 40 package-years who stopped the day before his lung transplantation? Does “HIV” mean a well controlled infection while on long-lasting, successful antiretroviral therapy or an untreated case of AIDS? Unfortunately, many researchers tend to combine these cases, in order to get larger numbers and to get their paper published.

Second, there are numerous confounding factors to consider. In some case series, only symptomatic patients are described, in others only those who were hospitalized (and who have *per se* a higher risk for severe disease). In some countries, every patient with SARS-CoV-2 infection will be hospitalized, in others only those with risk factors or with severe COVID-19. Testing policies vary widely between countries. The control group (with or without comorbidities) is not always well-defined. Samples may not be representative, risk factors not correctly taken into account. Sometimes, there is incomplete information about age distribution, ethnicity, comorbidities, smoking, drug use and gender (there is some evidence that, in female patients, comorbidities have no or less impact on the course of the disease, compared to male (Meng 2020)). All these issues present important limitations and only a few studies have addressed all of them.

Third, comorbidity papers have led to an information overload. Yes, virtually every medical discipline and every specialist has to cope with the current pandemic. And yes, everybody has to be alert these days, psychiatrists as well as esthetic surgeons. Hundreds of guidelines or position papers have been published, trying to thoughtfully balance fear of COVID-19 against the dire consequences of not treating other diseases than COVID-19 in an effective or timely manner – and all this in the absence of data. On May 15, a PubMed search yielded 530 guidelines or considerations about specific diseases in the context of COVID-19, among them those for grade IV glioma (Bernhardt 2020, bottom line: do not delay treatment), but also for dysphonia and voice rehabilitation (Mattei 2020: can be postponed), infantile hemangiomas (Frieden 2020: use telehealth), ocular allergy (Leonardi 2020: very controversial), high resolution anoscopy (Mistrangelo 2020: also controversial), migraine management (Szperka 2020: use telehealth) and breast reconstruction (Salgarello 2020: defer “whenever possible”), to name just a few. These recommendations are usually not helpful. They apply for a few weeks, during acute health crisis scenarios as seen in overwhelmed health care systems in Wuhan, Bergamo, Madrid or New York. In other cities or even a few weeks later, proposed algorithms are already outdated. Nobody needs a 60-page recommendation, concluding that “clinical judgment and decision making should be exercised on a case-by-case basis”.

However, some important papers have been published during the last months, a couple of them with very helpful data, supporting the management of patients with comorbidities. In the following, we will briefly go through these.

Hypertension and cardiovascular comorbidities

From the beginning of the pandemic, hypertension and/or cardiovascular disease (CVD) have been identified as potential risk factors for severe disease and death (Table 1). However, all studies were retrospective, included only hospitalized patients and did not distinguish between uncontrolled and controlled hypertension or used different definitions for CVD. Multivariate analyses adjusting for confounders were performed in only a few studies. Moreover, different outcomes and patient groups were analyzed. According to some experts, current data do not necessarily imply a causal relationship between hypertension and severity of COVID-19. There is no study that demonstrates the independent predictive value of hypertension. It is “unclear whether uncontrolled blood pressure is a risk factor for acquiring COVID-19, or whether controlled blood pressure among patients with hypertension is or is not less

of a risk factor” (Schiffrin 2020). The same applies to CVD, with the difference that the numbers here are even lower.

From a mechanistic point of view, however, it seems plausible that patients with underlying cardiovascular diseases and pre-existing damage to blood vessels such as atherosclerosis may face higher risks for severe diseases. During recent weeks, it has become clear that SARS-CoV-2 may directly or indirectly attack the heart, kidney and blood vessels. Various cardiac manifestations of COVID-19 do occur contemporarily in many patients (see chapter *Clinical Presentation*, page 279). Infection may lead to cardiac muscle damage, blood vessel constriction and to elevated levels of inflammation-inducing cytokines. These direct and indirect adverse effects of the virus may be especially deleterious in those with already established heart disease. During the next months, we will learn more about the role and contributions of arteriosclerosis in the pathogenesis of COVID-19.

Table 1. Hypertension in larger cohort studies, prevalence and outcome

Study	Setting	Hypertension present?	Multivariate, hazard or odds ratio (95% CI) for endpoint
Wang 2020	344 ICU pts, Tongji, China	Survivors vs Non-Survivors: 34 vs 52%	Not done
Grasselli 2020	521 ICU pts, 72 hospitals in Italy	Discharge from ICU vs death at ICU: 40 vs 63%	Not done
Guan 2020	1,099 hospitalized pts, 522 hospitals in China	Non-severe disease vs severe: 13 vs 24%	Not done
Zhou 2020	191 hospitalized pts from Jinyintan and Wuhan	Survivors vs Non-Survivors: 23 vs 48%	Not done
Shi 2020	487 hospitalized pts in Zhejiang Province	Non-severe disease at admission vs severe: 17 vs 53%	OR 2.7 (1.3-5.6) for severe disease at admission
Guan 2020	1,590 hospitalized pts, 575 hospitals in China	Non-severe vs severe courses: 13 vs 33%	HR 1.6 (1.1-2.3) for severe course (ICU, IMV, death)
Goyal 2020	393 hospitalized pts, 2 hospitals in New York	No IMV vs IMV during stay: 48 vs 54%	Not done

IMV invasive mechanical ventilation, ICU intensive care units

Treatment of hypertension during the pandemic

There has hardly been a topic that has kept doctors and their patients as busy as the question of whether antihypertensive drugs such as ACE inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) can cause harm to patients. The uncontrolled observations of increased mortality risk in patients with hypertension, CVD (see above) and diabetes raised concerns. These conditions share underlying renin-angiotensin-aldosterone system pathophysiology that may be clinically insightful. In particular, activity of the angiotensin-converting enzyme 2 (ACE2) is dysregulated (increased) in cardiovascular disease ([Vaduganathan 2020](#)). As SARS-CoV-2 cell entry depends on ACE2 ([Hoffmann 2020](#)), increased ACE2 levels may increase the virulence of the virus within the lung and heart.

ACEIs or ARBs may alter ACE2, and variation in ACE2 expression may in part be responsible for disease virulence. However, the first substantial study to examine the association between plasma ACE2 concentrations and the use of ACEIs/ARBs did not support this hypothesis: in two large cohorts from the pre-COVID-19 era, plasma concentrations of ACE2 were markedly higher in men than in women, but not with ACEI/ARB use ([Sama 2020](#)). A recent review of 12 animal studies and 12 human studies overwhelmingly implies that administration of both drug classes does not increase ACE2 expression ([Sriram 2020](#)).

However, some concerns on deleterious effects remain and some media sources and even scientific papers have called for the discontinuation of these drugs. This is remarkable as clinical data actually points in the opposite direction. Although all were observational (with the possibility of confounding), their message was consistent - none showed any evidence of harm.

- Among 2573 COVID-19 patients with hypertension from New York City, there were no differences in the likelihood for severe COVID-19 for different classes of antihypertensive medications – ACE inhibitors, ARBs, beta blockers, calcium channel blockers, and thiazide diuretics ([Reynolds 2020](#)).
- Comparing 6272 Italian cases (positive for SARS-CoV-2) to 30,759 controls (matched for sex, age, and municipality of residence), no evidence was found that ACE inhibitors or ARBs modify susceptibility to COVID-19 ([Mancia 2020](#)). The results applied to both sexes as well as to younger and older persons.
- In a retrospective study from Denmark (one of the countries with the best epidemiological data) of 4480 COVID-19 patients, prior ACEI/ARB use, compared with no use, was not significantly associated with mortality. In

a nested case-control study of a cohort of 494,170 patients with hypertension, use of ACEI/ARB, compared with use of other antihypertensive medications, was not significantly associated with COVID-19 diagnosis ([Fosbøl 2020](#)).

In conclusion, ACE inhibitors and/or ARBs should not be discontinued. Several randomized trials plan to evaluate ACEIs and ARBs for treatment of COVID-19 ([Mackey 2020](#)). According to a brief review, adjuvant treatment and continuation of pre-existing statin therapy could improve the clinical course of patients with COVID-19, either by their immunomodulatory action or by preventing cardiovascular damage ([Castiglioni 2020](#)). In a retrospective study on 13,981 patients in Hubei Province, China, the use of statins was independently associated with lower all-cause mortality (5.2% versus 9.4%). Randomized controlled trials involving statin treatment for COVID-19 are needed.

Treatment of coronary heart disease during the pandemic

Pre-existing cardiovascular disease is linked with higher morbidity and mortality in patients with COVID-19, whereas COVID-19 itself can induce myocardial injury, arrhythmia, acute coronary syndrome and venous thromboembolism (nice review: [Nishiga 2020](#)). Myocardial injury, evidenced by elevated cardiac biomarkers, was recognized among early cases and myocardial infarction (STEMI or NSTEMI) and may represent the first clinical manifestation of COVID-19. Of note, a culprit lesion is often not identifiable by coronary angiography. In a study of 28 patients with STEMI, this was the case in 39% ([Stefanini 2020](#)). According to the authors, a dedicated diagnostic pathway should be delineated for COVID-19 patients with STEMI, aimed at minimizing procedural risks and healthcare providers' risk of infection. There are already preliminary reports on a significant decline of 32% in the number of percutaneous coronary interventions for acute coronary syndromes ([Piccolo 2020](#)). Other authors have suggested that, in settings with limited resources to protect the work force, fibrinolytic therapies may be preferred over primary percutaneous coronary interventions ([Daniels 2020](#)).

Of note, several studies have found a spectacular drop in admissions for STEMI during the peak of the epidemic. In France a steep decline of 25% was found for both acute (< 24hrs) and late presentation (> 24 hrs) STEMI ([Rangé 2020](#)). Similar observations have been made in Italy ([De Filippo 2020](#)) and the US ([Solomon 2020](#)). Possible explanations for this phenomenon may be patients' fear of coming to the hospital or disturbing busy caregivers, especially in the case of mild STEMI clinical presentation. Other hypothetical reasons are reduced air pollution, better adherence to treatment, limited physical activity or absence of occupational stress during lockdown. However, there is

some evidence that the lower incidence does not reflect a true decline but just one more collateral damage of the pandemic. For example, Italian researchers have found a 58% increase of out-of-hospital cardiac arrests in March 2020 compared to the same period in 2019 (Baldi 2020). In New York, this increase seemed to be even more pronounced (Lai 2020). Others have observed an increased observed/expected mortality ratio during the early COVID-19 period indicating that patients try to avoid hospitalization (Gluckman 2020).

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Diabetes mellitus

Diabetes mellitus is a chronic inflammatory condition characterized by several macrovascular and microvascular abnormalities. As with hypertension and CVD, many of the above cited studies have also revealed that diabetic patients were overrepresented among the most severely ill patients with COVID-19 and those succumbing to the disease. Among the 23,698 in-hospital COVID-19-related deaths during the first months in the UK, a third occurred in people with diabetes: 7,434 (31.4%) in people with type 2 diabetes, 364 (1.5%) in those with type 1 diabetes (Barron 2020).

Current data suggest that diabetes in patients with COVID-19 is associated with a two-fold increase in mortality as well as severity of COVID-19, as compared to non-diabetics. In a meta-analysis of 33 studies and 16,003 patients (Kumar 2020), diabetes was found to be significantly associated with mortality from COVID-19 with a pooled odds ratio of 1.90 (95% CI: 1.37-2.64). Diabetes was also associated with severe COVID-19 and a pooled odds ratio of 2.75 (95% CI: 2.09-3.62). The pooled prevalence of diabetes in patients with COVID-19 was 9.8% (95% CI: 8.7%-10.9%). However, it is too early to say whether diabetes is acting as an independent factor responsible for COVID severity and mortality or if it is just a confounding factor.

A large retrospective study on the impact of type 2 diabetes (T2D) carefully analyzed 7337 cases of COVID-19 in Hubei Province, China, among them 952 with pre-existing T2D (Zhu 2020). The authors found that subjects with T2D required more medical interventions and had a significantly higher mortality (7.8% versus 2.7%; adjusted hazard ratio, 1.49) and multiple organ injury than non-diabetic individuals. Of note, well-controlled blood glucose was associated with markedly lower mortality (in-hospital death rate 1.1% versus 11.0%) compared to individuals with poorly controlled blood glucose. Similar results were found in a large UK cohort (Holman 2020).

A recent review has made some suggestions on the possible pathophysiological mechanisms of the relationship between diabetes and COVID-19, and its management (Hussain 2020). Rigorous glucose monitoring and careful consideration of drug interactions might attenuate worsening of symptoms and adverse outcomes. In a retrospective cohort study of 1213 hospitalized individuals with COVID-19 and pre-existing T2D, metformin use was significantly associated with a higher incidence of acidosis, particularly in cases with severe COVID-19, but not with 28-day COVID-19-related mortality (Cheng 2020).

Some treatment strategies for COVID-19 such as steroids and lopinavir/r bear a risk for hyperglycemia. On the other hand, hydroxychloroquine may improve glycemic control in decompensated, treatment-refractory patients with diabetes (Gerstein 2002, Rekedal 2010). However, it remains unclear which COVID-19 treatment strategy works best and if treatment of diabetic patients has to be different from those without diabetes. It is also unclear whether specific diabetes drugs such as DPP4 inhibitors increase or decrease the susceptibility or severity of SARS-CoV-2 infection.

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COPD and smoking

Chronic Obstructive Pulmonary Disease (COPD) is a common and preventable dysfunction of the lung associated with limitation in airflow. It is a complex disease associated with abnormalities of the airway and/or alveoli which is predominantly caused by exposure to noxious gases and particulates over a long period. A meta-analysis of 15 studies, including a total of 2473 confirmed COVID-19 cases showed that COPD patients were at a higher risk of more severe disease (calculated RR 1.88) and with 60% higher mortality (Alqahtani 2020). Unfortunately, the numbers in this review were very small and only 58 (2.3%) had COPD.

A meta-analysis of 5 early studies comprising 1399 patients observed only a trend but no significant association between active smoking and severity of COVID-19 (Lippi 2020). However, other authors have emphasized that current data do not allow to draw firm conclusions about the association of severity of COVID-19 with smoking status (Berlin 2020). In a more recent review, current smokers were 1.45 times more likely to have severe complications compared to former and never smokers. Current smokers also had a higher mortality rate (Alqahtani 2020).

Ever-smoking increased pulmonary ACE2 expression by 25% (Cai 2020). The significant smoking effect on ACE2 pulmonary expression may suggest an increased risk for viral binding and entry of SARS-CoV-2 into the lungs of smokers. Cigarette smoke triggers an increase in ACE2 positive cells by driving secretory cell expansion (Smith 2020). The overabundance of ACE2 in the lungs of smokers may partially explain a higher vulnerability of smokers.

However, it's not that easy – both quitting smoking and finding clinical correlations to the above cell experiments. Within a surveillance center primary care sentinel network, multivariate logistic regression models were used to identify risk factors for positive SARS-CoV-2 tests (Lusignan 2020). Of note,

active smoking was associated with decreased odds (yes, decreased: adjusted OR 0.49, 95% CI 0.34–0.71). According to the authors, their findings should not be used to conclude that smoking prevents SARS-CoV-2 infection, or to encourage ongoing smoking. Several explanations are given, such as selection bias (smokers are more likely to have a cough, more frequent testing could increase the proportion of smokers with negative results). Active smoking might also affect RT-PCR test sensitivity.

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HIV infection

HIV infection is of particular interest in the current crisis. First, many patients take antiretroviral therapies that are thought to have some effect against SARS-CoV-2. Second, HIV serves as a model of cellular immune deficiency. Third, and by far the most important point, the collateral damage caused by COVID-19 in the HIV population may be much higher than that of COVID-19 itself.

Preliminary data suggest no elevated incidence of COVID-19. In 5,700 patients from New York, only 43 (0.8%) were found to be HIV-positive (Richardson 2020). In Barcelona, the standardized incidence rate was lower in persons living with HIV (PLWH) than in the general population (Inciarte 2020). Given

the fact that HIV+ patients may be at higher risk for other infectious diseases such as STDs, these percentages were so low that some experts have already speculated on potential “protective” factors (i.e., antiviral therapies or immune activation). Moreover, a defective cellular immunity could paradoxically be protective for severe cytokine dysregulation, preventing the cytokine storm seen in severe COVID-19 cases.

Appropriately powered and designed studies that are needed to draw conclusions on the effect of COVID-19 are still lacking. However, our own retrospective analysis of 33 confirmed SARS-CoV-2 infections between March 11 and April 17 in 12 participating German HIV centers revealed no excess morbidity or mortality (Haerter 2020). The clinical case definition was mild in 25/33 cases (76%), severe in 2/33 cases (6%), and critical in 6/33 cases (18%). At the last follow up, 29/32 of patients with documented outcome (90%) had recovered. Three out of 32 patients had died. One patient was 82 years old, one had a CD4 T cell count of 69/ μ l and one suffered from several comorbidities. A similar observation was made in Milan, Italy, where 45/47 patients with HIV and COVID-19 (only 28 with confirmed SARS-CoV-2 infection) recovered (Gervasoni 2020). In another single center study from Madrid on 51 HIV patients with COVID-19 (35 confirmed cases), six patients were critically ill and two died (Vizcarra 2020). In these studies, as in our cohort, severe immune deficiency was rare. During recent months, there has been growing evidence that HIV+ patients with uncontrolled viremia and/or low CD4 cells are at higher risk for severe disease. In a large population study from South Africa, HIV was independently associated with increased COVID-19 mortality, showing an adjusted hazard ratio for mortality of 2.14 for HIV (95% CI 1.70-2.70) (Bouille 2020). Among 286 HIV-infected patients who were included by US healthcare providers, mortality rates were higher in patients with low CD4 counts (< 200 cells/mm³) (Dandachi 2020).

There is still an ongoing debate about potential effects of antiretroviral therapies against SARS-CoV-2. For lopinavir/r (and darunavir/r), there is now strong evidence that they don't work (see *Treatment* chapter, page 331). An ART regimen should not be changed to include a PI to prevent or treat COVID-19 (EACS 2020, US 2020). Tenofovir alafenamide (TAF) has some chemical similarities to remdesivir and has been shown to bind to SARS-CoV-2 RNA polymerase (RdRp) with high binding energies, and has been suggested as a potential treatment for COVID-19 (Elfiky 2020). In Spain, a large randomized Phase III placebo-controlled study (EPICOS, NCT04334928) compares the use of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC), hydroxychloroquine or the combination of both versus placebo as prophylaxis for COVID-19 in healthcare workers. Our observation that the majority (22/33) of HIV+ pa-

tients with COVID-19 were treated with tenofovir, including those developing severe or critical disease, indicate no or only minimal clinical effect against SARS-CoV-2 (Härter 2020). In the cohorts from Milan and Madrid, there was no evidence that any specific antiretroviral drug (such as tenofovir or PIs) affected COVID-19 susceptibility or severity (Gervasoni 2020, Vizcarra 2020). Most patients, however, have received TAF and not TDF for which preliminary data from Spain suggest a beneficial effect. Of 77,590 HIV+ persons receiving ART in Spain, 236 were diagnosed with COVID-19, 151 were hospitalized, 15 were admitted to the ICU, and 20 died (Del Amo 2020). The risk for COVID-19 hospitalization was higher among patients receiving TAF/FTC and ABC/3TC, compared to those receiving TDF/FTC. However, residual confounding by co-morbid conditions cannot be completely excluded. In a small group from France, attack rates were not lower with TDF/FTC in PrEP users (Charre 2020).

The most serious concern regarding HIV, however, is the collateral damage induced by COVID-19. In Western countries, there exist few reports of HIV+ patients having problems in gaining access to their HIV medications or having trouble taking them due to COVID-19 or the plans to manage it (Sanchez 2020). In contrast, disruption to delivery of health care in sub-Saharan African settings could well lead to adverse consequences beyond those from COVID-19 itself. Lockdown, transport restrictions and fear of coronavirus infection have already led to a dramatic drop in HIV and TB patients collecting medication in several African countries (Adepoju 2020). Using five different existing mathematical models of HIV epidemiology and intervention programmes in sub-Saharan Africa, investigations have already estimated the impact of different disruptions to HIV prevention and treatment services. Predicted average relative excess in HIV-related deaths and new HIV infections (caused by unsuppressed HIV RNA during treatment interruptions) per year over 2020-2024 in countries in sub-Saharan Africa that would result from 3 months of disruption of HIV-specific services, were 1.20-1.27 for death and 1.02-1.33 for new infections, respectively. A 6-month interruption of ART would result in over 500,000 excess HIV deaths in sub-Saharan Africa (range of estimates 471,000 - 673,000). Disrupted services could also reverse gains made in preventing mother-to-child transmission. According to WHO, there is a clear need for urgent efforts to ensure HIV service continuity and preventing treatment interruptions due to COVID-19 restrictions in sub-Saharan Africa.

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Immunosuppression (other than HIV)

Immunosuppression may bear a higher risk for SARS-CoV-2 infection and severe COVID-19. But the story is not that simple. Neither is it clear what immunosuppression actually means, nor are the available data sufficient to draw any conclusion. We just don't know enough. Nevertheless, some authors are trumpeting the news that there is an increased risk. A bad example? A systematic review and meta-analysis on 8 studies and 4,007 patients came to the conclusion that "immunosuppression and immunodeficiency were associated with increased risk of severe COVID-19 disease, although the statistical differences were not significant" (Gao 2020). The authors also state that "in response to the COVID-19 pandemic, special preventive and protective measures should be provided." There is null evidence for this impressive statement. The total number of patients with immunosuppression in the study was 39 (without HIV: 11!), with 6/8 studies describing less than 4 patients with different modalities of immunosuppression.

Despite the large absence of data, numerous viewpoints and guidelines have been published on how to manage immunosuppressed patients that may be more susceptible to acquire COVID-19 infection and develop severe courses. There are recommendations for intranasal corticosteroids in allergic rhinitis (Bousquet 2020), immunosuppressants for psoriasis and other cutaneous diseases (Conforti 2020, Torres 2020), rheumatic diseases (Favalli 2020, Figueroa-Parra 2020) or inflammatory bowel diseases (Kennedy 2020, Pasha 2020). The bottom line of these heroic attempts to balance the risk of immune-modifying drugs with the risk associated with active disease: what is generally needed, has to be done (or to be continued). Exposure prophylaxis is important.

However, several studies have indeed found evidence for deleterious effects of glucocorticoids, indicating that these drugs should be given with particular caution these days.

- In 600 COVID-19 patients with rheumatic diseases from 40 countries, multivariate-adjusted models revealed a prednisone dose ≥ 10 mg/day to be associated with higher odds of hospitalization. There was no risk with conventional disease-modifying anti-rheumatic drugs (DMARD) alone or in combination with biologics and Janus kinase (JAK) inhibitors (<https://doi.org/10.1136/annrheumdis-2020-217871>).
- In 525 patients with inflammatory bowel disease (IBD) from 33 countries (Brenner 2020), risk factors for severe COVID-19 included systemic corti-

costeroids (adjusted odds ratio 6.9, 95% CI 2.3-20.5), and sulfasalazine or 5-aminosalicylate use (aOR 3.1). TNF antagonist treatment was not associated with severe COVID-19.

- In 86 patients with IBD and symptomatic COVID-19, among them 62 receiving biologics or JAK inhibitors, hospitalization rates were higher in patients treated with oral glucocorticoids, hydroxychloroquine and methotrexate but not with JAK inhibitors (Haberman 2020).

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Cancer

Providing continuous and safe care for cancer patients is challenging in this pandemic. Oncologic patients may be vulnerable to infection because of their underlying illness and often immunosuppressed status and may be at increased risk of developing severe complications from the virus. On the other hand, the COVID-19 triage and management may stretch an already fragile system and potentially leave uncovered some vital activities, such as treatment administration or surgeries. It is well established that suboptimal timing and delayed oncologic treatment may lead to disease progression, leading to worse survival outcomes. There are several recommendations to minimising exposure of oncology patients to COVID-19 without compromising oncological outcome: Radiation for breast cancer (Coles 2020), hematopoietic cell transplantation (Dholaria 2020) and leukemia treatment (Zeidan 2020).

What is known about risk factors, besides general risk factors such as age, male gender and other comorbidities?

- Compared to 519 statistically matched patients without cancer, 232 patients from Wuhan were more likely to have severe COVID-19 (64% vs 32%). An advanced tumour stage was a risk factor (odds ratio 2.60, 95% CI 1.05–6.43) (Tian 2020).
- A systematic review of all studies until June 3 indicated that patients with hematological malignancies, especially those diagnosed recently (and likely those with myeloid malignancies), were at increased risk of death with COVID-19 compared to the general population. The evidence that this risk is higher than for those with solid malignancies was conflicting (El-Sharkawi 2020).
- Patients with Chronic Lymphatic Leukemia (CLL) seem to be at particular high risk of death. Of 198 CLL patients diagnosed with symptomatic COVID-19, 39% were treatment-naïve (“watch and wait”) while 61% received at least one CLL therapy. At 16 days, the overall CFR was 33%, while another 25% were still in hospital (Mato 2020).
- In a retrospective study from Italy, including 536 patients with a diagnosis of a hematological malignancy, 198 (37%) had died. Progressive disease status, diagnosis of acute myeloid leukemia, indolent or aggressive NHL were associated with worse overall survival (Passamonti 2020).
- In a large cohort study of 928 cancer patients with COVID-19 from the USA, Canada, and Spain, most prevalent malignancies were breast (21%)

and prostate (16%). In total 121 (13%) patients had died. Independent risk factors were an ECOG status of 2 or higher and “active” cancer ([Kuderer 2020](#)).

- SARS-CoV-2 viral load in nasopharyngeal swab specimens of 100 patients with cancer who were admitted to three New York City hospitals predicted outcome. The authors also found that patients with hematologic malignancies had higher median viral loads than patients without cancer ([Westblade 2020](#)).

Does anti-neoplastic treatment lead to increased risk of complications?

- Among a total of 309 patients, cytotoxic chemotherapy administered within 35 days of a COVID-19 diagnosis was not significantly associated with a severe or critical COVID-19 event. However, patients with active hematologic or lung malignancies, lymphopenia, or baseline neutropenia had worse COVID-19 outcomes.
- Among 423 cases of symptomatic COVID-19 patients, 40% were hospitalized and 12% died within 30 days. Age older than 65 years and treatment with immune checkpoint inhibitors were predictors for hospitalization and severe disease, whereas receipt of chemotherapy and major surgery were not ([Robilotti 2020](#)).

All these studies are not controlled. A myriad of potential factors may lead to a difference in COVID-19 outcomes and risk for patients with malignancies, compared to the rest of the population (nice review: [El-Sharkawi 2020](#)). These include patient behaviour (exposure to the virus?), healthcare professional behaviour (i.e., testing patients with a history of cancer for COVID-19 more frequently?), biological differences but also several confounders (more comorbidities, older age in cancer patients). Continued analysis of the data is required to attain further understanding of the risk factors for cancer patients in this pandemic.

Finally, it's not only treatment, it's also diagnosis. Diagnostic delays may lead to an increase in the numbers of avoidable cancers ([Maringe 2020](#)). During the pandemic, a large cross-sectional study in the US has observed significant declines in several cancer types, ranging from 24.7% for pancreatic cancer to 51.8% for breast cancer, indicating that a delay in diagnosis will likely lead to presentation at more advanced stages and poorer clinical outcomes ([Kaufman 2020](#)).

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Transplantation

During a health crisis such as the COVID pandemic, it is crucial to carefully balance cost and benefits in performing organ transplantation (Andrea 2020). There is no doubt that the current situation has deeply affected organ dona-

tion and that this represents an important collateral damage of the pandemic. All Eurotransplant countries have implemented preventive screenings policies for potential organ donors. For detailed information on the national policy, please visit <https://www.eurotransplant.org/2020/04/07/covid-19-and-organ-donation/>. Preliminary data indicate a significant reduction in transplantation rates even in regions where COVID-19 cases are low, suggesting a global and nationwide effect beyond the local COVID-19 infection prevalence (Loupy 2020). During March and April, the overall reduction in deceased donor transplantations since the COVID-19 outbreak was 91% in France and 51% in the USA, respectively. In both France and the USA, this reduction was mostly driven by kidney transplantation, but a substantial effect was also seen for heart, lung, and liver transplants, all of which provide meaningful improvement in survival probability. Solid organ transplant recipients are generally at higher risk for complications of respiratory viral infections (in particular influenza), due to their chronic immunosuppressive regimen, and this may hold particularly true for SARS-CoV-2 infection. The first cohort of COVID-19 in transplant recipients from the US indeed indicated that transplant recipients appear to have more severe outcomes (Pereira 2020). Some key studies:

Liver: In the largest cohort, 16/100 patients died from COVID-19. Of note, mortality was observed only in patients aged 60 years or older (16/73) and was more common in males than in females (Belli 2020). Although not statistically significant, more patients who were transplanted at least 2 years earlier died than did those who received their transplant within the past 2 years (18% vs 5%). A systematic search on June 15 revealed 223 liver transplant recipients with COVID-19 in 15 studies (Fraser 2020). The case fatality rate was 19.3%. Dyspnea on presentation, diabetes mellitus, and age 60 years or older were significantly associated with increased mortality ($p=0.01$) with a trend to a higher mortality rate observed in those with hypertension and those receiving corticosteroids at the time of COVID-19 diagnosis. However, in a multicenter cohort study, comparing 151 adult liver transplant recipients from 18 countries with 627 patients who had not undergone liver transplantation, liver transplantation did not significantly increase the risk of death in patients with SARS-CoV-2 infection (Webb 2020).

Kidney: In a single center with 36 kidney transplant recipients, 10/36 died (Akalın 2020). Patients appear to have less fever as an initial symptom, lower CD4 and CD8 T cell counts and more rapid clinical progression.

Heart: In a case series of 28 patients who had received a heart transplant in a large academic center in New York, 22 patients (79%) were hospitalized. At the end of the follow-up, 4 remained hospitalized and 7 (25%) had died (Latif

2020). In Germany, mortality was also high, and 7/21 patients died (Rivinius 2020).

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Other comorbidities

Ultimately, the current situation might lead to substantial changes in how research and medicine are practiced in the future. The SARS-CoV-2 pandemic has created major dilemmas in almost all areas of health care. Scheduled operations, numerous types of treatment and appointments have been cancelled world-wide or postponed to priorities hospital beds and care for those who are seriously ill with COVID-19. Throughout the world, health systems had to consider rapidly changing responses while relying on inadequate information. In some settings such as HIV or TB infection, oncology or solid organ transplantation, these collateral damages may have been even greater than the damage caused by COVID-19 itself. Treatment interruptions, disrupted

drug supply chains and consequent shortages will likely exacerbate this issue. During the next months, we will learn more and provide more information on the consequences of this crisis on various diseases.

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11. Pediatrics

Tim Niehues

Jennifer Neubert

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SARS-CoV-2 infection in children

Children are less susceptible to SARS-CoV-2 infection, have a lower seroprevalence and a less severe COVID-19 disease course than adults ([Castagnoli 2020](#), [Viner 2020](#), [Merckx 2020](#), [Zimmermann 2020](#), [Parri 2020](#), [Ludvigsson 2020](#)). In this regard, COVID is strikingly different from other virus-induced respiratory diseases, which can be fatal in children (e.g. RSV in infants). The CoV-2 pandemic causes a large collateral damage to children because they are taken out of their normal social environment (kindergartens, schools etc.), and because of parents' resistance to seek medical care despite need e.g. for vaccination ([Bramer 2020](#)) or even if their children are having an emergency ([Lazzerini 2020](#)).

Common coronaviruses in children: tropism, incubation period and spreading

The first International Corona Virus Conference was organized by Volker Termeulen in Würzburg/Germany in 1980. At the time only one human coronavirus, HCoV2229E, was known to be associated with the common cold ([Weiss 2020](#)). Commonly circulating human coronaviruses (CoV) can be isolated from 4-8% of all children with acute respiratory tract infections, which tend to be mild, unless the child is immunocompromised ([Ogimi 2019](#)). Seven coronaviruses circulate among humans ([Hufert 2020](#)): α -Coronaviruses HCoV-229e (discovered in 1966), HCoV-NL63 (in 2004); β -Coronaviruses HCoV-OC43 (in 1967)-HKU1 (in 2005), -OC43; MERS-CoV (in 2012), SARS-CoV (in 2003) and SARS-CoV-2 that originally derive from bats (NL63, 229e, SARS-CoV), dromedary camels (229e, MERS-CoV), cattle (OC43) and pangolins (SARS-CoV-2) ([Zimmermann 2020](#)). There appear to be re-infections with the earlier described common COV despite the fact that most individuals seroconvert to human coronaviruses. In many children there are co-infections with other viruses such as Adeno-, Boca-, Rhino-, RSV-, Influenza- or Parainfluenza vi-

rus. There seems to be a cyclical pattern with seasonal outbreaks between December and May or March to November in the southern hemisphere.

Single-strand RNA coronaviruses are capable of mutation and recombination leading to novel coronaviruses that can spread from animals to humans. They have caused epidemics leading to significant case fatality rates (10% in SARS-CoV, Hong Kong 2002; more than 30% in MERS-CoV, Saudi Arabia 2012). Because of the high case fatality rate, both SARS-CoV and MERS-CoV have a low potential for long-term sustained community transmission. Accordingly, no human SARS-CoV infections have been reported since July 2003.

It is estimated that in SARS-CoV-2, one person infects 2-3 other persons. In clusters (e.g. nosocomial outbreaks) this number might be much higher. In both SARS-CoV and MERS-CoV, super-spreading events with one individual infecting up to 22 (SARS) or even 30 individuals (MERS) have been reported, especially in nosocomial outbreaks. In SARS-CoV a total of 41 children were reported with no deaths. Similarly, in MERS-CoV only 38 children were reported in two studies, with two deaths (Zimmermann 2020).

Epidemiology of COVID-19 in children

On April 6 the US CDC reported 2572 (1.7%) children under 18 years among 149,082 reported cases from 12 February to 2 April 2020. The availability of data was extremely limited (less than 10% available on symptoms, 13% on underlying conditions, 33% on whether children were hospitalized or not). Three deaths were reported to the CDC but no details were given. The median age was 11 and they were 57% males. 15 children were admitted to an ICU ($\leq 2\%$). Children < 1 year accounted for the highest percentage (15-62%) of hospitalization (CDC 2020). The Chinese CDC report (Dong 2020) comprises 2143 pediatric patients from January 16 to February 8 2020. Only 731 children (34,1%) were laboratory confirmed cases. The median age was 7 years with 56,6% boys, less than 5% were classified as severe and less than 1% as critical.. The Korean Center for Disease Control and Prevention reported on 20 March that 6.3% of all COVID-19 cases were children under 19 years of age; again, the children had a mild form of the disease (Korean Center for Disease Control and Prevention. Press releases, <https://www.cdc.go.kr>). Italian data published on 18 March showed that only 1,2% of the 22,512 Italian cases with COVID-19 were children; no deaths were reported in this and in the Spanish cohort from Madrid (2 March to 16 March) (Livingstone 2020, Tagarro 2020). In Germany, 9657 children and adolescents with COVID-19 were reported up to May 4th, 2020; only 128 were admitted to 66 hospitals, only one child died (Armman 2020).

The European Surveillance System (TESSy) collects data from EU/EEA countries and the UK on laboratory-confirmed cases of COVID-19. Out of 576,024 laboratory confirmed COVID-19 cases 0,7% were 0-4 years, 0,6% 5-9 years, 0,9% 10-14 years (<https://covid19-surveillance-report.ecdc.europa.eu>). The multicentre cohort study (82 participating health-care institutions across 25 European countries), Paediatric Tuberculosis research Network (ptbnet) confirmed that COVID-19 is generally a mild disease in children. Of 582 children and adolescents (median age 5.0 years, 25% with pre-existing conditions) with PCR-confirmed SARS-CoV-2 infection, 363 (62%) were admitted to hospital and 48 (8%) required ICU admission. Significant risk factors for requiring ICU admission in multivariate analyses were being younger than 1 month (odds ratio 5.1), male sex (2.1) and pre-existing medical conditions (3.3). Four children died (Göttinger 2020).

Natural course and risk factors for complications

The incubation period is believed to be 3-7 days (range 1-14 days) (She 2020), the clinical onset 5-8 days after infection with the virus. Children often have an asymptomatic or less severe COVID-19 disease course than adults (Zimmermann 2020, Parri 2020). Among a total of 100 children with SARS-CoV-2 from Italy, 21% were asymptomatic, 58% had mild disease, 19% had moderate disease, 1% had severe disease, and 1% were in critical condition (Parri 2020).

Due to the paucity of data it is as yet unclear which group of children may be at a higher risk for development of complications, e.g. children with underlying chronic pulmonary or cardiac disease, severe neurologic deficits, immunosuppressed or critically ill children, etc. Analogous to influenza there might be genetic susceptibility in some children (see below, pathophysiology, Clohisey 2019). Interestingly, in a flash survey from 25 countries with 10,000 children with cancer at risk and 200 tested, only 9 were found to be CoV-2 positive. They were asymptomatic or had mild disease (Hrusak 2020). Even in the severely immunosuppressed and in children with significant cardiac and pulmonary comorbidities COVID-19 can be overcome (Dinkelbach 2020).

In The European Surveillance System (TESSy) deaths among children aged below 15 years are rare, 4 out of 44,695 (0.009%) were reported. The rate of hospitalization was higher in children under the age of five especially in infants compared to persons aged 5-29. However, it is believed that the threshold for admission is lower in young children. A severe course requiring admission to ICU seems not to be more likely in younger children. The likelihood of being hospitalised was higher when children had an underlying con-

dition, and a severe course was rare (<https://covid19-surveillance-report.ecdc.europa.eu>).

In a cross-sectional study including 48 children with COVID-19 (median age 13 years; admitted to 46 North American pediatric ICUs between March 14 and April 3, 2020), forty patients (83%) had significant pre-existing co-morbidities and 18 (38%) required invasive ventilation. Targeted therapies were used in 28 patients (61%, mainly HCQ). Two patients (4%) died and 15 (31%) were still hospitalized, with 3 still requiring ventilatory support and 1 receiving ECMO (Shekerdeman 2020). In an observational retrospective cohort study that included 177 children and young adults with clinical symptoms and laboratory confirmed SARS-CoV-2 infection treated between March 15 and April 30, 2020 at the Children's National Hospital in Washington, 44 were hospitalized and 9 were critically ill. Of these, 6/9 were adolescents and young adults > 15 years of age. Although asthma was the most prevalent underlying condition overall, it was not more common among patients with severe disease (DeBiasi 2020).

Although the natural course of COVID-19 is uneventful in most pediatric patients, a very small percentage can develop a potentially fatal severe hyperinflammatory state 2-4 weeks after acute infection with SARS-CoV-2 (Riphagen 2020). This hyperinflammatory state is termed as pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS) (or synonym Multisystem Inflammatory Syndrome in Children (MIS-C). Of the 570 MIS-C cases reported to the CDC by July 2020, 10 patients had died (1.8%) and 364 (63.9%) patients required treatment in an intensive care unit. Obesity was the most commonly reported underlying medical condition (Godfred-Cato 2020).

Pathophysiology and immunopathology

It is unclear why COVID-19 in children is associated with a less severe disease course.

The tissue expression pattern of the receptor for CoV-2 angiotensin converting enzyme (ACE2) and the transmembrane serine protease TMPRSS2 (essential for CoV-2 cell entry) as well as the tissue tropism of CoV-2 in childhood are unknown but age-dependent differences in ACE2 receptor expression may explain why outcomes differ in children versus adults (Bunyavanich 2020).

ACE2 is expressed on cells of the airways, the lungs, mucosal cells (lids, eyelids, nasal cavities), intestines and on immune cells (monocytes, lymphocytes, neutrophils) (Molloy 2020, reviewed in Brodin 2020). It needs to be clarified

whether there is neurotropism (e.g. affecting the developing brain of newborns).

The main target of CoV-2 is the respiratory tract. As respiratory infections are extremely common in children it is to be expected that there are other viruses present in the respiratory tract of young children concomitantly with the coronavirus, which may limit its growth and the number of CoV-2 copies in the respiratory tract of children. Systematic viral load measurements in the respiratory tract of different viruses in children are underway. Key to the later immunopathologic stages of COVID-19 pneumonia is the macrophage activation syndrome (MAS)-like hyperinflammatory phase with a cytokine storm and acute respiratory distress syndrome (ARDS), usually within 10-12 days after symptom onset. In general, children are not less prone to develop ARDS during respiratory tract infections than adults. In the H1N1 flu pandemic in 2009, being under the age of 1 year was a significant risk factor for developing a severe form of the infection and ARDS (Bautista 2010). Why ARDS is less common in children compared to adults with COVID-19 is unclear. SARS-CoV-2 infection of cardiac tissue can be a major contributor to fatal myocarditis (Dolhnikoff 2020, Prieto 2020).

An explanation for the milder disease course in children could be age-related differences in innate or adaptive immune responses to CoV-2 between adults and children. In the innate immune response to any virus, Type I (IFN α , IFN β) and type III (IFN Ω) interferons are the most important cytokines. In 659 patients (1 month to 99 years old) with life-threatening COVID-19 pneumonia, inborn defects in the type 1 IFN signaling were found in 23 unrelated patients (Zhang 2020). Moreover, neutralizing auto-antibodies to type I/III IFN were found in 101/987 patients with life-threatening COVID-10 pneumonia (Bastard 2020). These findings show that inborn defects in the IFN I/II pathway or auto-antibodies to IFN I/III may predispose to life-threatening COVID-19. Based on influenza animal models it has been proposed that BCG vaccination (for tuberculosis prevention, done in the first week of life in some countries) may enhance non-specific innate immunity in children to infections like COVID-19 (so-called trained immunity) (Moorlag 2019). A search of the BCG World Atlas and correlation with data of COVID-19 cases and death per country found that countries without universal policies of BCG vaccination (Italy, the Netherlands, USA) have been more severely affected compared to countries with universal and long-standing BCG policies and that BCG vaccination also reduced the number of reported COVID-19 cases in a country (Miyasaka 2020, Hauer 2020). Recent data from a large population-based study did not show decreased infection rates in Israeli adults aged 35 to 41 years who were BCG-vaccinated in childhood as compared to non-BCG-

vaccinated. Data on the effect of BCG vaccination on COVID-19 disease severity are unavailable (Hamiel 2020).

In the adaptive response to any virus, cytotoxic T cells play an important role in regulating responses to viral infections and control of viral replication. Children could benefit from the fact that the cytotoxic effector function of CD8 T cells in viral infection in children may be less detrimental compared to adults. Immune dysregulation with exhaustion of T cells has been reported in adults with COVID-19 infection. Regarding humoral immunity, IgG maternal antibodies are actively transferred to the child via placenta and/or IgA via breast milk. They may not include anti CoV-2 antibodies, if the mother is naïve to CoV-2 or infected late in pregnancy. In mothers with COVID-19 pneumonia serum and throat swabs of their newborns were negative for CoV-2 but virus-specific IgG antibodies were detected (Zeng H 2020). Thus, neonates may benefit from placental transmission of virus-specific antibodies from pre-exposed mothers. As shown in SARS CoV-1 it is likely that in SARS-CoV-2 a newly infected child will mount a significant humoral response with neutralizing IgM (within days) and IgG antibodies (within 1-3 weeks) to one of the immunodominant epitopes, e.g. the crown-like spike proteins giving the coronaviruses their name. Infections with non-SARS COV are very common in children (see above); however, to what extent previous infections with non-SARS coronaviruses may have led to protective cross-reactive antibodies is unclear.

Data regarding IgG and IgM seroprevalence and quality of the immune response in children are lacking. No human re-infections with CoV-2 have been demonstrated yet but overall it is not clear whether children mount a durable memory immune response to CoV-2. In summary, differences in the immune system such as more efficient innate and adaptive immunity to COV-2 (associated with better thymic function), cross-reactive immunity to common cold coronaviruses and differences in the ACE2 receptor expression as well as better overall health may be factors leading to a better COVID-19 outcome in children (Consiglio 2020).

Transmission

Studies on the risk of acquiring SARS-CoV-2 infection in children in comparison to adults have shown contradicting results (Mehta 2020, Gudbjartsson 2020, Bi 2020). The exact role that children play in the transmission of SARS-CoV-2 is not yet fully understood. Population based studies performed so far indicate that children might not play a major factor in the spreading of COVID-19 (Gudbjartsson 2020).

Vertical transmission

Contraction of COVID-19 in a pregnant woman may have an impact on fetal outcome, namely fetal distress, potential preterm birth or respiratory distress if the mother gets very sick. Schwartz reviewed 5 publications from China and was able to identify 38 pregnant women with 39 offspring among whom 30 were tested for COVID-19 and all of them were negative (Schwartz 2020, Chen 2020). Among the 24 infants born to women with COVID-19, 15 (62.5%) had detectable IgG and 6 (25.0%) had detectable IgM; nucleic acid test results were all negative. Among 11 infants tested at birth, all had detectable IgG and 5 had detectable IgM. IgG titers with positive IgM declined more slowly than those without (Gao 2020). In the PRIORITY study (n = 263), adverse outcomes, including preterm birth, NICU admission, and respiratory disease, did not differ between infants born to mothers testing positive for SARS-CoV-2 (n = 184) and those born to mothers testing negative (n = 79), suggesting that infants born to mothers infected with SARS-CoV-2 generally do well in the first 6-8 weeks after birth (Flaherman 2020).

Transmission of COVID-19 appears unlikely to occur if correct hygiene precautions are undertaken. In 1481 deliveries at three hospitals in New York City, 116 (8%) mothers tested positive for SARS-CoV-2; 120 neonates were identified and none were positive for SARS-CoV-2 (Salvatore 2020).

In another study from New York, 101 newborns of SARS-CoV-2 infected mothers no transmission was observed despite sleeping in the same room and breastfeeding (Dumitriu 2020). Initially it was thought that CoV-2 is not vertically transmitted, but in a more recent analysis of 31 mothers with SARS-CoV-2, SARS-CoV-2 genome was detected in one umbilical cord blood, two at-term placentas, one vaginal mucosa and one breast-milk specimen. Three cases of vertical transmission of SARS-CoV-2 have been documented (Fenizia 2020).

In a UK national population-based cohort study on SARS-CoV-2 infected pregnant women, twelve (5%) of 265 infants subsequently tested positive for SARS-CoV-2 RNA, six of them within the first 12 hours after birth (Knight 2020). Postpartum acquisition appears to be the most common mode of infection; in a recent review only 4/1141 neonates born to SARS-CoV-2 infected mothers were thought to have a congenital infection (Dhir 2020).

Horizontal transmission

Culture-competent SARS-CoV-2 has been grown from the nasopharynx of symptomatic neonates, children, and adolescents: 12 (52%) of 23 symptomatic SARS-CoV-2-infected children, the youngest being 7 days old. SARS-CoV-2 viral load and shedding patterns of culture-competent virus in the 12 symp-

tomatic children resembled those in adults. Systematic measurements of SARS-CoV-2 viral load measurements in children are lacking. Therefore, transmission of SARS-CoV-2 from children is plausible (L'Huillier 2020). SARS-CoV-2 in children is transmitted through family contacts and mainly through respiratory droplets (Garazzino 2020). In a study from France, child-to-child and child-to-adult transmission seems to be uncommon (Danis 2019). Prolonged exposure to high concentrations of aerosols may facilitate transmission (She 2020).

SARS-CoV-2 may theoretically also be transmitted through the digestive tract. ACE2 is also found in upper esophageal and epithelial cells as well as intestinal epithelial cells in the ileum and colon (She 2020). SARS-CoV-2 RNA can be detected in the feces of patients (Holshue 2020). Cai revealed that viral RNA is detected from feces of children at a high rate (and can be excreted for as long as 2-4 weeks) (Cai 2020). However, direct evidence of a fecal-to-oral transmission has not yet been documented.

Onward transmission from children to others is low (Viner 2020, Merckx 2020). In a study from Milan, Italy, in 83 children and 131 adults hospitalized and symptomatic in regard to COVID-19, adults were retrospectively more likely to be CoV-2 positive, asymptomatic carriers as compared to children (9% vs 1%) (Milani 2020).

Diagnosis and classification

Testing for the virus is only necessary in clinically suspect children. If the result is initially negative, repeat nasopharyngeal or throat swab testing of upper respiratory tract samples or testing of lower respiratory tract samples should be done. Sampling of the lower respiratory tract (induced sputum or bronchoalveolar lavage) is more sensitive (Han 2020). This is not always possible in critically ill patients and in young children.

Diagnosis is usually made by real-time polymerase chain reaction RT-PCR on respiratory secretions. For SARS-CoV, MERS-CoV and SARS-CoV-2, higher viral loads have been detected in samples from lower respiratory tract compared with upper respiratory tract.

In some patients, SARS-CoV-2 RNA is negative in respiratory samples while stool samples are still positive indicating that a viral gastrointestinal infection can last even after viral clearance in the respiratory tract. (Xiao 2020). Fecal testing may thus be of value in diagnosing COVID-19 in these patients.

As in other viral infections, a CoV-2 IgM and IgG seroconversion will appear in days (IgM) to 1-3 weeks (IgG) after infection and may or may not indicate protective immunity (still to be determined). Interestingly, asymptomatic

seroconversion has been hypothesized in a very small series of health workers (mean age 40 years) exposed to a child with COVID-19 in a pediatric dialysis unit (Hains 2020).

Serology may be useful in patients with clinical symptoms highly suggestive of SARS-CoV-2 who are RNA negative, i.e in children with pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS). If serology indicates protective immunity, this will be extremely important from a public health perspective, e.g. it will allow for strategic staffing in medical care and for the assessment of CoV-2 epidemiology (herd immunity).

Table 1. COVID classification in children (Shen 2020)

1	Asymptomatic without any clinical symptoms
2	Mild fever, fatigue, myalgia and symptoms of acute respiratory tract infections
3	Moderate pneumonia, fever and cough, productive cough, wheezing but no hypoxemia
4	Severe fever, cough, tachypnea, oxygen saturation less than 92%, somnolence
5	Critical quick progress to acute respiratory distress syndrome (ARDS) or respiratory failure

Laboratory and radiology findings

Laboratory and/or radiology studies in outpatient children who have mild disease are not indicated. Upon admission to the hospital the white blood cell count is usually normal. In a minority of children decreased lymphocyte counts have been documented. In contrast, adults (with hyperinflammation and cytokine release syndrome) often have an increase in neutrophils and lymphopenia. The inflammation parameters C reactive protein and procalcitonin can be slightly elevated or normal while there are elevated liver enzymes, creatine kinase CK-MB and D dimers in some patients. LDH appears to be elevated in severe cases and can be used to monitor severe disease.

A chest X-ray should only be done in children with moderate or more severe disease as CT scans mean a very high radiation exposure for the child and should only be done in complicated or high-risk cases. In the beginning of the pandemic in China, children all received CT scans even when they were asymptomatic and oligosymptomatic; surprisingly, they displayed very severe changes. On chest radiography there are bilateral patchy airspace consolidations and so-called ground-glass opacities. CT scans were more impressive

than chest x-ray examinations. In 20 children with CT, 16 (80%) had some abnormalities (Xia 2020).

Symptoms and signs: Acute infection

Children and adolescents

In a clinical trial of 171 children from Wuhan, fever was reported in 41% (71 of 171), cough in over 50% (83 of 171), tachypnea in 28% (49 of 171). In 27 of the patients there were no symptoms at all (15,8%). At initial presentation very few children required oxygen supplementation (4 of 171, 2,3%). Other symptoms like diarrhea, fatigue, runny nose and vomiting were observed in less than 10% of the children (Lu 2020). In the cohort from Zhejiang as many as 10 out of 36 patients (28%) had no symptoms at all. None of the children had an oxygen saturation below 92% (Qiu 2020). In a Korean case series of children with COVID-19, 20 children (22%) were asymptomatic during the entire observation period. Among 71 symptomatic cases, only 6 (9%) were diagnosed at the time of symptom onset while 47 children (66%) had unrecognized symptoms before diagnosis and 18 (25%) developed symptoms after diagnosis. Fifty-one percent had “mild” disease, 22% “moderate” disease and 2% “severe” disease. No patient required intensive care (Han 2020). A larger UK series reports on 651 children and young people aged less than 19 years. Median age was 4.6 years, 35% (225/651) were under 12 months old. 18% (116/632) of children were admitted to critical care. Six patients died in hospital, all of whom had profound comorbidity (Swann 2020).

A recent comprehensive systematic review analysed 131 studies in 7780 pediatric COVID-19 patients across 26 different countries (Hoang 2020). In this review 19,3% of the patients were asymptomatic, the most common symptoms were fever (59%), cough (55,9%), rhinorrhea (20%) and myalgia/fatigue (18,7%). The need for intensive care treatment was low (3,3%).

In 52 hospitalized children from London, UK, renal dysfunction was frequent especially in those with pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2. 24 (46%) had elevated serum creatinine, and 15 (29%) met the diagnostic criteria for acute kidney injury (Stewart 2020).

In a case series of 4 children with PIMS-TS (see below) from London, UK, neurological symptoms were described (encephalopathy, headaches, brainstem and cerebellar signs, muscle weakness, reduced reflexes) with signal changes in the splenium of the corpus callosum on neuroimaging and required intensive care admission for the treatment of COVID-19 pediatric multisystem inflammatory syndrome (Abdel-Mannan 2020).

Neonates and infants

Zeng reports 33 newborns born to mothers with COVID-19 in Wuhan. Three of the 33 infants (9%) presented with early-onset SARS-CoV-2 infection. In 2 of the 3 neonates there were radiological signs of pneumonia. In one child disseminated intravascular coagulation was described but eventually all children had stable vital signs three weeks after the infection (Zeng L 2020). In a second cohort, 9 infants aged 1 month to 9 months were described without any severe complications (Wei 2020). Whether there are long-term complications of COVID-19 in these newborns and infants is unclear at this stage of the pandemic.

Pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS) (or synonym Multisystem Inflammatory Syndrome in Children (MIS-C) or Kawasaki-like Disease

While most children with COVID-19 have a very mild disease, in April 2020 clinicians from the UK, France, Italy, Spain and the US reported on children with a severe inflammatory syndrome with Kawasaki-like features, some of whom had tested positive for CoV-2, while others not. Prior to this, Jones had described the case of a six-month-old baby girl with fever, rash and swelling characteristic of a rare pediatric inflammatory condition, Kawasaki disease (Jones 2020).

Eight patients from the UK and 10 patients from Bergamo in Italy with features of Kawasaki disease were published including one death in a 14-year-old boy in the UK during the SARS-CoV-2 epidemic (Riphagen 2020, Verdoni 2020). Some children presented with vasculitic skin rash (Schneider 2020). In Bergamo, the region with the highest infection rate in Italy, a 30-fold increased incidence of Kawasaki disease has been reported following the SARS-CoV-2 epidemic (Verdoni 2020). Of 21 children and adolescents from London, UK (19 with recent SARS-CoV-2 infection), 12 (57%) presented with Kawasaki disease shock syndrome, 16 (76%) with myocarditis, 17 (81%) required intensive care support. All had noticeable gastrointestinal symptoms and high levels of inflammatory markers, received intravenous immunoglobulin and 10 (48%) corticosteroids; the outcome was favourable in all (Toubiana 2020).

In the UK, 78 of the PIMS-TS cases reported 36 (46%) were invasively ventilated, 28 (36%) had evidence of coronary artery abnormalities, three children needed ECMO and two children died (Davies 2020).

In another study from the UK, 50% of the 58 “PIMS-TS” cases developed shock and required inotropic support or fluid resuscitation; 22% met diagnostic cri-

teria for Kawasaki disease; and 14% had coronary artery dilatation or aneurysms (Whittaker 2020).

In a US MIS-C study on 186 patients 131 (70%) were positive for SARS-CoV-2 by RT-PCR or antibody testing. Detailed analysis of clinical manifestation revealed the gastrointestinal system (92%), cardiovascular (80%), hematologic (76%), mucocutaneous (74%), and respiratory involvement (70%). In total, 148 patients (80%) received intensive care, 37 (20%) received mechanical ventilation, and 4 (2%) died. Coronary-artery aneurysms were documented in 15 patients (8%), and Kawasaki disease-like features were documented in 74 (40%) (Feldstein 2020). In the largest cohort to date,

570 US MIS-C patients were reported as of July 29. A total of 203 (35.6%) of the patients had a typical MIS-C clinical course (shock, cardiac dysfunction, abdominal pain, and markedly elevated inflammatory markers) and almost all had positive SARS-CoV-2 test results (Class 1). The remaining 367 (64.4%) of MIS-C patients (Class 2 and 3) had manifestations that appeared to overlap with acute COVID-19 or had features of Kawasaki disease. 364/570 patients (63.9%) required care in an intensive care unit. Ten patients (1.8%) died. Approximately two thirds of the children had no pre-existing underlying medical conditions (Godfred-Cato 2020).

In summary, the pathophysiological overlap between COVID-19-associated inflammation and Kawasaki disease is not yet clear, their features are summarized in Table 2. The main pathophysiological differences appear to be an IL17A-driven inflammation in Kawasaki disease (KD) and a stronger endothel activation in coronary artery involvement in MIS-C. In both, MIS-C and KD autoantibodies may play an important role and MIS-C patients show distinct CD4 subset abnormalities. (Consiglio 2020).

Table 2. Features of Kawasaki Disease and pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2

	Kawasaki (Hedrich 2017, ECDC 2020) (previously called mucocutaneous lymph-node syndrome)	PIMS-TS (pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 or MIS-C (multisystem inflammatory syndrome in children) (Verdoni 2020 ; Riphagen 2020 , https://covid19-surveillance-report.ecdc.europa.eu/) “ Kawasaki-like disease ”
Epidemiology	Incidence 5–19/100,000 annually < 5 years of age (EU, US), in north-east Asia higher; seasonal increase in winter/spring, geographic wave-like spread of illness during epidemics (Rowley 2018)	Incidence unknown 230 suspected cases temporally associated with COVID-19 reported to ECDC by May 15 th (EU/EEA, UK). More common in afro-caribbean descent, obesity? (Riphagen 2020)
Age, sex	>90% < 5 years of age, more males	5-15 years of age, sex distribution unclear
Etiology	Unknown, hypothesis: infection with common pathogens, e.g. bacteria, fungi and viruses which cause immune-mediated damage (Dietz 2017) (Jordan-Villegas 2010 , Kim 2012 , Turnier 2015). Genetic factors (increased frequency in Asia and among family members of an index case)	Unknown, no working hypothesis yet. Hyperinflammation/shock associates with immune response to SARS-CoV-2. In CoV-1 antibody-dependent enhancement (ADE): presence of antibodies can be detrimental, enable the virus to spread (demonstrated in SARS-CoV)
Case definition	fever ≥5 days, combined with at least 4 of the 5 following items 1. Bilateral bulbar conjunctival injection 2. Oral mucous membrane changes, including injected or fissured lips, injected pharynx, or strawberry tongue 3. Peripheral extremity changes, including erythema of palms or soles, edema of hands or feet (acute phase) or periungual desquamation (convalescent phase) 4. Polymorphous rash	1. Persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with other additional clinical, laboratory or imaging and ECG features. Children fulfilling full or partial criteria for Kawasaki Disease may be included 2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus 3. SARS-CoV-2 PCR testing positive or negative (Royal College of Paediatrics and Child Health)

Table 2. Features of Kawasaki Disease and pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2

<p>5. Cervical lymphadenopathy (McCrindle 2017)</p> <p>Children suspected of having KD who do not fulfill diagnostic criteria may have incomplete or atypical KD (Cimaz 2009)</p>		
CoV-2 status in most cases	CoV-2 Ag (PCR); Abs (Elisa) negative	CoV-2 Ag (PCR) negative and Abs (Elisa) positive
Typical Lab	<p>Marked Elevation of acute-phase reactants (eg, C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR])</p> <p>Thrombocytosis (generally after day 7 of illness)</p> <p>Leukocytosis, left-shift (increased immature neutrophils)</p>	<p>Marked elevation of acute phase reactants CRP, ESR</p> <p>Thrombocytopenia</p> <p>Leucopenia</p> <p>Lymphopenia</p> <p>Hyperferritinemia</p> <p>Elevated myocarditis markers Troponin, pro-BNP</p>
Acute Complications	<p>Kawasaki disease shock syndrome (KSSS) (rare), features of macrophage activation syndrom, MAS (rare), coronary artery abnormalities, mitral regurgitation, prolonged myocardial dysfunction, disseminated intravascular coagulation (Kanegaye 2009)</p> <p>Gastrointestinal complications (Ileitis, vomiting, abdominal pain) rare</p>	<p>Shock (common), features of macrophage activation syndrome (common), myocardial involvement evidenced by markedly elevated cardiac enzymes (common), myocardial infarction, aneurysms, disseminated intravascular coagulation</p> <p>Gastrointestinal complications (Ileitis, vomiting, abdominal pain) are very common</p>
Long term Complications	<p>Artery abnormalities (aneurysms of mid-sized arteries, giant coronary artery aneurysms CAAs)</p>	<p>Aneurysms</p>
Management	<p>High-dose intravenous immunoglobulin (IVIG) (2g/kg) first-line treatment; effective in reducing the risk of coronary</p>	<p>So far, most patients published were treated with high dose IVIG, glucocorticoids, ASS (Verdoni 2020, Riphagen 2020, Ahmed 2020)</p> <p>IVIG resistance requiring adjunctive steroid</p>

Table 2. Features of Kawasaki Disease and pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2

	artery disease when administered within 10 days of onset of fever. In addition, acetylsalicylic acid, glucocorticoids and anti-TNF monoclonal antibodies have been used	treatment is common (Verdoni 2020,) Management on the pediatric intensive care unit is often necessary: progression to vasoplegic shock is common Hemodynamic support, treatment with noradrenaline and milrinone, mechanical ventilation is often required (Riphagen 2020)
Prognosis	Self-limited vasculitis lasting for an average of 12 days without therapy. Without timely treatment, CAAs, and in particular aneurysms, can occur in up to 25% of children	Overall prognosis not yet clear More severe course than KD Potentially fatal in individual cases

Management

National guidelines and guidance documents have been published from different medical societies in China, North America, Italy, UK and Germany (<https://rcpch.ac.uk>; Venturini 2020, Chiotos 2020, Liu 2020; <https://www.rcpch.ac.uk/key-topics/covid-19>; <https://dgp.de/stellungnahme-medikamentoesse-behandlung-von-kindern-mit-covid-19/>)

Infection control in the medical setting

Early identification of COVID-19 and quarantine of contacts is imperative. In the in- and out-patient setting it is advised to separate children who have infectious diseases from healthy non-infectious children. Nosocomial outbreaks have played a role in the clustering of COVID-19. It is advised to admit children with COVID-19 to the hospital only if an experienced pediatrician feels it is medically necessary (e.g. tachypnea, dyspnea, oxygen levels below 92%). In the hospital the child with COVID-19 or suspicion of COVID-19 needs to be isolated in a single room or admitted to a COVID-19-only ward in which COVID-19-exposed medical personnel is protected by non-pharmacological interventions (wearing FFP-2 masks, gowns, etc.) and maintains distance and is cohorted themselves (e.g. no shifts on other wards). The presence of one parent is not negotiable in the care of the sick child both for emotional reasons as well as for help in the nursing of the child.

At present it is not recommended to separate healthy newborns from mothers with suspicion of COVID-19 (CDC-2 2020). Clearly, a preterm or newborn

that has been exposed to CoV-2 needs to be closely monitored by the hospital and/or the primary care pediatrician. If there are signs of COVID (e.g. poor feeding, unstable temperature, tachy/dyspnea) it needs to be hospitalized and tested and lab examinations and chest x-ray to be done. Testing for CoV-2 is not useful before day 5 because of the incubation period. There needs to be strict hygiene as much as possible in this mother-child setting.

During peak phases of the COVID-19 pandemic, precautions in the outpatient and hospital setting include entrance control, strict hand and respiratory hygiene, daily cleaning and disinfection of the environment, and provision of protection (gloves, mask, goggles) for all medical staff when taking care of a COVID-19 or a suspected COVID-19 case (Wang 2020). In neonatal intensive care units (NICU), negative pressure rooms and filtering of exhaust would be ideal (Lu Q 2020). Respirators with closed circuit and filter systems should be used. Aerosol generating procedures, e.g. intubation, bronchoscopy, humidified inhalations/nebulization should be avoided as much as possible.

Infection control outside the medical setting

Some of the interventions to control the COVID pandemic have caused significant damage to children and adolescents. The description of their impact is beyond the scope of this article and reviewed elsewhere.⁴

Supportive treatment (respiratory support, bronchodilatation therapy, fever, superinfection, psychosocial support)

Having the child sitting in an upright position will be helpful for breathing. It might be useful to have physiotherapy. Insufflation of oxygen via nasal cannula will be important to children as it will increase lung ventilation and perfusion. In neonates, high flow nasal cannula (HFNC) has been utilized widely due to its superiority over other non-invasive respiratory support techniques.

The clinical use and safety of inhaling different substances is unclear in COVID-19. In other common obstructive and infectious childhood lung diseases, e.g. in bronchiolitis, the American Academy of Pediatrics is now recommending against the use of bronchodilators (Dunn 2020). Regarding the inhalation of steroids as part of maintenance therapy for asthma bronchiale there is no evidence to discontinue this treatment in children with COVID-19.

There is a large controversy over the extent of antipyretics usage in children. Still, in a child with COVID-19 who is clinically affected by high-degree fever,

⁴ Recommendations regarding attendance to kindergartens and schools have been published (Cohen 2020).

paracetamol or ibuprofen may be useful. There is no restriction despite initial WHO warnings of using ibuprofen, there is no evidence that the use of paracetamol or ibuprofen is harmful in COVID-19 in children (Day 2020).

The differentiation between CoV-2-induced viral pneumonia and bacterial superinfection is difficult unless there is clear evidence from culture results or typical radiological findings. Bacterial superinfection will be treated according to the international and national guidelines (Mathur 2018).

The virus outbreak brings psychological stress to the parents and family as well as medical staff; therefore, social workers and psychologists should be involved when available.

Treatment of respiratory failure

The treatment of pediatric acute respiratory distress syndrome (pARDS) is reviewed elsewhere (Allareddy 2019). For neonates with pARDS high-dose pulmonary surfactant replacement, nitric oxide inhalation, and high-frequency oscillatory ventilation might be effective. In critically ill neonates, continuous renal replacement and extracorporeal membrane oxygenation need to be implemented if necessary.

COVID-19-specific drug treatment

As of yet there are no data from controlled clinical trials and thus there is currently no high-quality evidence available to support the use of any medication to treat COVID-19. The drugs listed below are repurposed drugs and there is limited or almost no pediatric experience. In the case of a severe or critically ill child with COVID the pediatrician has to make a decision whether to try a drug or not. If initiation of a drug treatment is decided, children should be included into clinical trials (<https://www.clinicaltrialsregister.eu>) if at all possible. However, there are very few, if any, studies open for recruitment in children.

When to treat with drugs

Under the lead of the German Society for Pediatric Infectiology (DGPI) an expert panel has proposed a consensus on when to start antiviral or immunomodulatory treatment in children (Table 3)).

A panel of pediatric infectious diseases physicians and pharmacists from North American institutions published an initial guidance on the use of antivirals for children with SARS. It is advised to limit antiviral therapy to children in whom the possibility for benefit outweighs the risk of toxicity and remdesvir is the preferred agent (Chiotos 2020).

Inhibitors of viral RNA synthesis

Remdesivir is available as 150 mg vials. Child dosing is

- < 40 kg: 5 mg/kg iv loading dose, then 2,5 mg/kg iv QD for 9 days
- ≥ 40 kg: 200 mg loading dose, then 100 mg QD for 9 days

Remdesivir is an adenosine nucleotide analogue with broad-spectrum antiviral activity against various RNA viruses. The compound undergoes a metabolic mechanism, activating nucleoside triphosphate metabolites for inhibiting viral RNA polymerases. Remdesivir has demonstrated *in vitro* and *in vivo* activity in animal models against MERS and SARS-CoV. Remdesivir showed good tolerability and a potential positive effect in regard to decrease of the viral load and mortality in Ebola in Congo in 2018 (Mulangu 2019). In Europe this drug has rarely been used in children so one should be extremely careful. It can be obtained through compassionate use programs (<https://rdvcu.gilead.com>).

Table 3. Consensus on antiviral or immunomodulatory treatment in children

Disease severity in child	Intervention
Mild or moderate disease pCAP, upper respiratory tract infection, no need for oxygen	Treat symptomatically No need for antiviral or immunomodulatory treatment
More severe disease and risk groups* pCAP, need for oxygen	Treat symptomatically Consider antiviral therapy
Critically ill, admitted to ICU	Treat symptomatically Consider antiviral therapy Consider immunomodulatory treatment
Secondary HLH (hemophagocytic lymphohistiocytosis)	Treat with immunomodulatory or immunosuppressive drugs

* Congenital heart disease, immunosuppression, inborn/acquired immunodeficiencies, cystic fibrosis, chronic lung disease, chronic neurological/kidney/liver disease, diabetes/metabolic disease

Lopinavir/r (LPV/r, Kaletra®) is a co-formulation of lopinavir and ritonavir, in which ritonavir acts as a pharmacokinetic enhancer (booster). LPV/r is an HIV-1 protease inhibitor successfully used in HIV-infected children as part of highly active antiretroviral combination therapy (PENTA Group, 2015). In the SARS epidemics, LPV/r was recommended as a treatment. A recent study in adult COVID-19 patients did not show an effect regarding the primary end point in a controlled clinical trial. Despite the fact that there is long experience with LPV/r in HIV, **it is not advised to use it in children with COVID-**

19 as it does not appear to be effective at all (see *Treatment* chapter, page 331)

Inhibitors of viral entry

Hydroxychloroquine (HCQ, Quensyl®), Chloroquine (CQ, Resochin junior®, Resochin®) The experience among pediatricians with HCQ/CQ (except pediatricians working with malaria) is very limited. Authorities in the US are now warning about a widespread use of HCQ/CQ in COVID-19 (<https://mailchi.mp/clintox/aact-acmt-aapcc-joint-statement>). **It is not advised to use HCQ or CQ in children with COVID as neither drug appears to be effective at all (see *Treatment* chapter, page 331).**

Immunomodulatory drug treatment

The rationale for immunomodulation in COVID-19 adult patients comes from a high expression of pro-inflammatory cytokines (Interleukin-1 (IL-1) and interleukin-6 (IL-6)), chemokines (“cytokine storm”) and the consumption of regulatory T cells resulting in damage of the lung tissue as reported in patients with a poor outcome. In children, the proinflammatory cytokines TNF and IL-6 do not appear to be central in CoV-2 induced hyperinflammation ([Consiglio 2020](#)). **Blocking IL-1 or IL-6** can be successful in children with (auto) inflammatory disease (reviewed in [Niehues 2019](#)), but both interleukins are also key to the physiological immune response and severe side effects of immunomodulators have been reported. In adults with COVID-19, blocking interleukin-1/6 might be helpful (see the *Treatment* chapter). **In the rare situation that the condition of the child deteriorates due to hyperinflammation and they are resistant to other therapies, anakinra may be an option as IL-1 seems to play a role in endothelial activation.**

Steroids (e.g. prednisone, prednisolone) are available as oral solution, tablets or different vials for intravenous application. Dosage in children is 0,5 to 1 mg/kg iv or oral BID. Short term use of steroids has few adverse events. Administration of steroids will affect inflammation by inhibiting the transcription of some of the pro-inflammatory cytokines and various other effects. Initially, the use of corticosteroids in children and adults with CoV-induced ARDS was controversial ([Lee 2004](#), [Arabi 2018](#), [Russell 2020](#)). Only in severe and critically ill children the use of dexamethasone appears justified in children. In adults, the use of steroids in severe COVID-19 is clearly beneficial although the corticosteroid-induced decrease of antiviral immunity (e.g. to eliminate CoV-2 viruses) might be theoretically disadvantageous. Data supporting the use of steroids in children with CoV-induced ARDS are lacking.

Only in severe and critically ill children might the use of dexamethasone appear justified.

Most patients with pediatric inflammatory multisystem syndrome associated with SARS-CoV-2 (PIMS-TS) published so far were treated with high dose IVIG and methylprednisolone (Verdoni 2020, Riphagen 2020). In these patients, features of macrophage activation syndrome and IVIG resistance were common, requiring adjunctive steroid treatment (Verdoni 2020). Clearly, any child severely affected by CoV-2 will need steroids at some stage.

Tocilizumab (Roactemra®) is available in 80/200/400 mg vials (20 mg/ml). Dosing is

- < 30 kg: 12 mg/kg iv QD, sometimes repeated after 8 hrs
- ≥ 30 kg: 8mg/kg iv QD iv (max. 800 mg)

Adverse events (deriving largely from long term use in chronic inflammatory diseases and use in combination with other immunomodulatory drugs): severe bacterial or opportunistic infections, immune dysregulation (anaphylactic reaction, fatal macrophage activation), psoriasis, vasculitis, pneumothorax, fatal pulmonary hypertension, heart failure, gastrointestinal bleeding, diverticulitis, gastrointestinal perforation (reviewed in Niehues 2019).

Anakinra (Kineret®) is available as 100 mg syringes (stored at 4-8° C). Dosing is 2-4 mg/kg sc QD daily as long as hyperinflammation persists. Thereafter, dose reduction by 10-30% per day. Higher dosage (> 4mg/kg-10mg/kg; max 400mg/d) may be necessary in patients with PIMS-TS. Adverse events (deriving largely from long-term use in chronic inflammatory diseases and use in combination with other immunomodulatory drugs): severe bacterial or opportunistic infections, fatal myocarditis, immune dysregulation, pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatitis, encephalitis, psoriasis, vitiligo, neutropenia (reviewed in Niehues 2019).

Immunotherapy

There are no systematic data on the use of convalescent plasma in children yet, but in a child with acute lymphoblastic leukemia and a young adult with a SCID (Severe Combined Immunodeficiency) phenotype and a high CoV-2 viral load, administration of convalescent plasma resulted in complete viral suppression (Shankar 2020, unpublished observation). Engineering **monoclonal antibodies** against the CoV spike proteins or against its receptor ACE2 or **specific neutralizing antibodies** against CoV-2 present in convalescent plasma may provide protection but are generally not available yet.

Interferon α has been inhaled by children with COVID-19 in the original cohorts but there are no data on its effect (Qiu 2020). Type I/III interferons (e.g.

interferon α) are central to antiviral immunity. When coronaviruses (or other viruses) invade the host, viral nucleic acid activates interferon-regulating factors like IRF3 and IRF7 which promote the synthesis of type I interferons (IFNs).

PIMS / MIS-C

Based on the information published so far, most patients were treated with high dose intravenous Immunglobulin (see Table 2) and corticosteroids (Verdoni 2020). More data are needed to determine the optimal treatment strategies for patients with MIS-C.

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12. The First Eight Months

Bernd Sebastian Kamps

Dezember - March

Sunday, 1 December

According to a retrospective study published in *The Lancet* on 24 January 2020⁵, the earliest laboratory confirmed case of COVID-19 in Wuhan was in a man whose symptoms began on 1 December 2019. No epidemiological link could be found with other early cases. None of his family became ill.

Thursday, 12 December

In **Wuhan**, health officials start investigating a cluster of patients with viral pneumonia. They eventually find that most patients have visits to the Huanan Seafood Wholesale Market in common. The market is known for being a sales hub for poultry, bats, snakes, and other wildlife.

Monday, 30 December 2019

Li Wenliang (en.wikipedia.org/wiki/Li_Wenliang), a 34-year-old ophthalmologist from Wuhan, posts a message on a WeChat group alerting fellow doctors to a new disease at his hospital in late December. He writes that seven patients have symptoms similar to SARS and are in quarantine. Li asks his friends to inform their families and advises his colleagues to wear protective equipment.

Tuesday, 31 December 2019

The Wuhan police announce that they are investigating eight people for spreading rumors about a new infectious diseases outbreak (see 30 December).

The Wuhan Municipal Health Commission [reports 27 patients](#) with viral pneumonia and a history of exposure to the Huanan Seafood Wholesale Mar-

⁵ Huang, Chaolin et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China January 24, 2020 [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30183-5/fulltext#%20](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30183-5/fulltext#%20)

ket. Seven patients are critically ill. The clinical manifestations of the cases were mainly **fever**, a few patients had **difficulty breathing**, and chest radiographs showed **bilateral lung infiltrative lesions**. The report says that the “disease is preventable and controllable”. WHO is informed about the outbreak.

Thursday, 1 January

The Huanan Seafood Wholesale Market is shut down.

Friday, 3 January

While examining bronchoalveolar lavage fluid collected from hospital patients between 24 and 29 December, Chinese scientists at the National Institute of Viral Disease Control and Prevention ruled out the infection with 26 common respiratory viruses, determined the genetic sequence of a novel β -genus coronaviruses (naming it '2019-nCoV') and identified three distinct strains.⁶

Li Wenliang is summoned to a local public security office in Wuhan for “spreading false rumours”. He is forced to sign a document where he admits having made “false comments” and “disrupted social order.” Li signs a statement agreeing not to discuss the disease further.

On the Weibo social network, Wuhan police say they have taken legal action against people who “published and shared rumors online”, “causing a negative impact on society”. The following day, the information is taken up by CCTV, the state television. CCTV does not specify that the eight people accused of “spreading false rumors” are doctors.

Sunday, 5 January

WHO issues an alert that 44 patients with pneumonia of unknown etiology have been reported by the national authorities in China. Of the 44 cases reported, 11 are severely ill while the remaining 33 patients are in stable condition. <https://www.who.int/csr/don/05-january-2020-pneumonia-of-unknown-cause-china/en/>

⁶ Notes from the Field: An Outbreak of NCIP (2019-nCoV) Infection in China — Wuhan, Hubei Province, 2019–2020, China CDC Weekly, 2020, 2(5): 79–80 <http://weekly.chinacdc.cn/en/article/id/e3c63ca9-dedb-4fb6-9c1c-d057adb77b57>

Tuesday, 7 January

Chinese officials announce that they have identified a **new coronavirus** (CoV) from patients in Wuhan (pre-published 17 days later: <https://doi.org/10.1056/NEJMoa2001017>). Coronaviruses are a group of viruses that cause diseases in mammals and birds. In humans, the most common coronaviruses (HCoV-229E, -NL63, -OC43, and -HKU1) continuously circulate in the human population; they cause colds, sometimes associated with fever and sore throat, primarily in the winter and early spring seasons. Two coronavirus have also been responsible for human outbreaks of SARS and MERS. These viruses are spread by inhaling droplets generated when infected people cough or sneeze, or by touching a surface where these droplets land and then touching one's face.

Friday, 10 January

The gene sequencing data of the new virus was posted on Virological.org by researchers from Fudan University, Shanghai. A further three sequences were posted to the Global Initiative on Sharing All Influenza Data (GISAID) [portal](#).

On 10 January 2020, Li Wenliang, coronavirus whistleblower, started having symptoms of a dry cough. Two days later, Wenliang started having a fever and was admitted to the hospital on 14 January 2020. His parents also contracted the coronavirus and were admitted to the hospital with him. Wenliang tested negative several times until finally testing positive for the coronavirus on 30 January 2020.

Sunday, 12 January

Using the genetic sequence of the new coronavirus made available to WHO, laboratories in different countries start producing specific **diagnostic PCR tests**.

The Chinese government reports that there is no clear evidence that the virus passes easily from person to person.

Monday, 13 January

Thailand reports the first case outside of China, a woman who had arrived from Wuhan. Japan, Nepal, France, Australia, Malaysia, Singapore, South Korea, Vietnam, Taiwan, and South Korea report cases over the following 10 days.

Tuesday, 14 January

WHO tweeted that “preliminary investigations conducted by the Chinese authorities have found no clear evidence of human-to-human transmission of the novel coronavirus (2019-nCoV) identified in Wuhan, China”. On the same day, WHO’s Maria Van Kerkhove said that there had been “limited human-to-human transmission” of the coronavirus, mainly small clusters in families, adding that “it is very clear right now that we have no sustained human-to-human transmission”⁷

Saturday, 18 January

The Medical Literature Guide **Amedeo** (www.amedeo.com) draws the attention of 50,000+ subscribers to a study from Imperial College London, *Estimating the potential total number of novel Coronavirus cases in Wuhan City, China*, by Imai et al. The authors estimate that “a total of 1,723 cases of 2019-nCoV in Wuhan City (95% CI: 427 – 4,471) had onset of symptoms by 12th January 2020”. Officially, only 41 cases were reported by 16th January.

Monday, 20 January

China reports three deaths and more than 200 infections. Cases are now also diagnosed outside Hubei province (Beijing, Shanghai and Shenzhen). Asian countries begin to introduce mandatory screenings at airports of all arrivals from high-risk areas of China.

After two medical staff were infected in Guangdong, the investigation team from China's National Health Commission confirmed for the first time that the coronavirus can be transmitted between humans.⁸

Wednesday, 22 January 2020

A WHO China office field mission to Wuhan issued a statement saying that there was evidence of human-to-human transmission in Wuhan, but more investigation was needed to understand the full extent of transmission.⁹

7 WHO says new China coronavirus could spread, warns hospitals worldwide". Reuters. 14 January 2020.

8 <https://www.theguardian.com/world/2020/jan/20/coronavirus-spreads-to-beijing-as-china-confirms-new-cases>

9 <https://www.who.int/china/news/detail/22-01-2020-field-visit-wuhan-china-jan-2020>

Thursday, 23 January

In a bold and unprecedented move, the Chinese government puts tens of millions of people in **quarantine**. Nothing comparable has ever been done in human history. Nobody knows how efficient it will be.

All events for the Lunar New Year (starting on January 25) are cancelled.

The WHO IHR (2005) Emergency Committee convened on 22-23 January acknowledged that human-to-human transmission was occurring with a preliminary R0 estimate of 1.4-2.5 and that 25% of confirmed cases were reported to be severe. However, the Committee felt that transmission was limited and there was “no evidence” of the virus spreading at community level outside of China. Since the members could not reach a consensus, the committee decided that it was still too early to declare a Public Health Emergency of International Concern (PHEIC) and agreed to reconvene in approximately ten days’ time.¹⁰

A scientific preprint from the Wuhan institute of Virology, later published in *Nature*, announced that a bat virus with 96% similarity had been sequenced in a Yunnan cave in 2013. The sequence is posted the next day on public databases.¹¹ It is confirmed that the novel coronavirus uses this same entry receptor as SARS-CoV.

Friday, 24 January

At least 830 cases have been diagnosed in nine countries: China, Japan, Thailand, South Korea, Singapore, Vietnam, Taiwan, Nepal, and the United States.

The first confirmed evidence of human-to-human transmission outside of China was documented by the WHO in Vietnam.¹²

France reported its first three confirmed imported cases, the first occurrences in the EU.¹³

Zhu et al. publish their comprehensive report about the isolation of a **novel coronavirus** which is different from both MERS-CoV and SARS-CoV (full-text:

¹⁰ [https://www.who.int/news-room/detail/23-01-2020-statement-on-the-meeting-of-the-international-health-regulations-\(2005\)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-\(2019-ncov\)](https://www.who.int/news-room/detail/23-01-2020-statement-on-the-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov))

¹¹ Zhou, Peng et al. "A pneumonia outbreak associated with a new coronavirus of probable bat origin". *Nature*. 579 (7798): 270-273 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7095418/>

¹² "Novel Coronavirus (2019-nCoV) SITUATION REPORT - 4" WHO 24 January 2020.

¹³ "Coronavirus : un troisième cas d'infection confirmé en France". *Le Monde.fr* (in French). 24 January 2020.

<https://doi.org/10.1056/NEJMoa2001017>). They describe sensitive assays to detect viral RNA in clinical specimens.

Huang et al. publish on *The Lancet* the **clinical features** of 41 patients (full-text: [doi.org/10.1016/S0140-6736\(20\)30185-9](https://doi.org/10.1016/S0140-6736(20)30185-9)). The report indicated the risk of contagious infection without forewarning signs during the incubation period and suggested a “pandemic potential” for the new virus.

Chan et al. describe a **familial cluster** of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission (full-text: [doi.org/10.1016/S0140-6736\(20\)30154-9](https://doi.org/10.1016/S0140-6736(20)30154-9)).

Saturday, 25 January

The Chinese government imposes travel restrictions on more cities in Hubei. The number of people affected by the quarantine totals **56 million**.

Hong Kong declares an emergency. New Year celebrations are cancelled and links to mainland China restricted.

Monday, 27 January

In Germany, the first cluster of infections with person to person transmission from asymptomatic patients in Europe **was reported**. The source of infection was an individual from Shanghai visiting a company in Bavaria¹⁴. She developed symptoms on the way back to China. Contacts at the company were tested and transmission was confirmed to asymptomatic contacts but also to people who had no direct contact with the index patient. Authors state that “The fact that asymptomatic persons are potential sources of 2019-nCoV infection may warrant a reassessment of transmission dynamics of the current outbreak.”¹⁵

Tuesday, 28 January

WHO DG Dr. Tedros Adhanom Ghebreyesus met China President Xi Jinping in Beijing. They shared the latest information on the outbreak and reiterated their commitment to bring it under control. The WHO delegation highly appreciated the actions China has implemented in response to the outbreak, its

¹⁴ Böhmer MM, Buchholz U, Cormann VM: **Investigation of a COVID-19 outbreak in Germany resulting from a single travel-associated primary case: a case series**. Published online May 15, 2020. Full-text: [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30314-5/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30314-5/fulltext)

¹⁵ Rothe C, Schunk M, Sothmann P, et al. **Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany**. *N Engl J Med* 2020;382:970-971. <https://pubmed.gov/32003551>. Full-text: <https://doi.org/10.1056/NEJMc2001468>

speed in identifying the virus and openness to sharing information with WHO and other countries.¹⁶

Thursday, 30 January

On the advice of the IHR Emergency Committee, WHO DG declared a Public Health Emergency of International Concern and advised “all countries should be prepared for containment, including active surveillance, early detection, isolation and case management, contact tracing and prevention of onward spread of 2019-nCoV infection, and to share full data with WHO.” WHO had received reports of 83 cases in 18 countries outside China and that there had been evidence of human-to-human transmission in 3 countries.

China reports 7,711 cases and 170 deaths. The virus has now spread to all Chinese provinces.

Giuseppe Conte, Italy’s Prime Minister, confirms the first two COVID-19 imported cases in Italy.

Friday, 31 January

Li Wenliang publishes his experience with **Wuhan police station** (see 3 January) with the letter of admonition on social media. His post goes viral.

India, the Philippines, Russia, Spain, Sweden, the United Kingdom, Australia, Canada, Japan, Singapore, the US, the UAE and Vietnam confirm their first cases.

Sunday, 2 February

The first death outside China, of a Chinese man from Wuhan, is reported in the **Philippines**. Two days later a death in Hong Kong is reported.

Thursday, 6 February

Li Wenliang, who was punished for trying to raise the alarm about coronavirus, dies. His death sparks an explosion of anger, grief and demands for freedom of speech: <https://www.theguardian.com/global-development/2020/feb/07/coronavirus-chinese-rage-death-whistleblower-doctor-li-wenliang>.

¹⁶ <https://www.who.int/news-room/detail/28-01-2020-who-china-leaders-discuss-next-steps-in-battle-against-coronavirus-outbreak>

Friday, 7 February

Hong Kong introduces **prison sentences** for anyone breaching quarantine rules.

Saturday, 8 February

The French Health Minister confirmed that a cluster of 5 COVID-19 cases were detected in a ski resort in the French Alps. The index patient was a UK citizen who had traveled to Singapore on 20-23 January and then spent four days (24-28 January) in a chalet in Contamines-Montjoie, in Haute-Savoie. He tested positive upon return to England. Four contacts in the same chalet tested positive, including a 9-year old boy who was attending a local school. None of the child's contacts in school or at home became infected.

Monday, 10 February

Amedeo launches a weekly Coronavirus literature service which would later be called **Amedeo COVID-19**.

Tuesday, 11 February

Less than three weeks after introducing mass quarantine measures in China, the number of daily **reported cases starts dropping**.

The WHO announces that the new infectious disease would be called **COVID-19 (Coronavirus disease 2019)** and that the new virus will be called SARS-CoV-2.

Wednesday, 12 February

On board the Diamond Princess **cruise ship** docked in Yokohama, Japan, 175 people are infected with the virus. Over the following days and weeks, almost 700 people will be infected onboard.

Thursday, 13 February

China changed the COVID-19 case definition to include clinical (radiological) diagnosis of patients without confirmatory test. As a result, Hubei reported 14,840 newly confirmed cases, nearly 10 times more than the previous day, while deaths more than doubled to 242. WHO indicated that for consistency it would report only the number of laboratory-confirmed cases.¹⁷

¹⁷ <https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200213-sitrep-24-covid-19.pdf>

Wednesday, 19 February

Iran reports two deaths from the coronavirus.

At the San Siro stadium in Milan, the Atalanta soccer team from Bergamo wins the Champions League match against Valencia 4 to 1 in front of 44,000 fans from Italy (2,000 from Spain). The mass transport from Bergamo to Milan and return, hours of shouting as well as the following festivities in innumerable bars have been considered by some observers as a coronavirus ‘biological bomb’.

Thursday, 20 February

A patient in his 30s tested positive for SARS-CoV-2 and was admitted to the intensive care unit (ICU) in **Codogno** Hospital (Lodi, Lombardy, Italy). The symptomatic patient had visited the hospital the day before but was not tested as he did not meet the suspected case epidemiological criteria (no link with China). His wife, 5 hospital staff, 3 patients and several contacts of the index patients also tested positive to the COVID-19. Over the next 24 hours, the number of reported cases would increase to 36, many without links to the Codogno patient or previously identified positive cases. A first COVID-19 death in a 78-year-old man was also reported. It is the beginning of the Italian epidemic. jamanetwork.com/journals/jama/fullarticle/2763188

Saturday, 22 February

South Korea reports a sudden spike of 20 new cases of coronavirus infection, raising concerns about a potential “super spreader” who has already infected 14 people in a church in the south-eastern city of Daegu.

Sunday, 23 February

Italy confirms 73 new cases, bringing the total to 152, and a third death, making Italy the third country in the world by number of cases, after China and South Korea. A “red zone” area around Codogno is created, isolating 11 municipal areas. Schools are closed.

Venice Carnival is brought to an early close and sports events are suspended in the most-hit Italian regions.

Monday, 24 February

France, Bahrain, Iraq, Kuwait, Afghanistan and Oman report their first cases.

Tuesday, 25 February

A report of a joint WHO mission of 25 international and Chinese experts is presented to the public. The mission travelled to several different Chinese provinces. The most important findings are that the Chinese epidemic peaked and plateaued between the 23rd of January and the 2nd of February and declined steadily thereafter (Table 1).

[https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-\(covid-19\)](https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19))

This was the first sign that the **aggressive use of quarantine** ordered by the Chinese government was the **right thing to do**. Unfortunately, European countries which did not experience the SARS epidemic in 2003, would lose precious time before following the Chinese example.

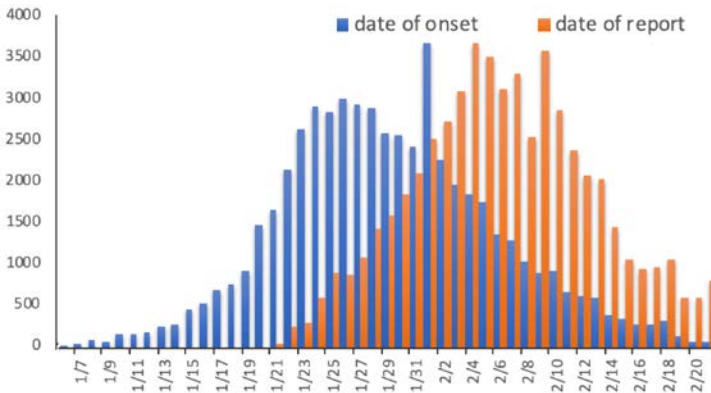


Figure 1. COVID-19 cases in China, January/February 2020. Epidemic curves by symptom onset and date of report on 20 February 2020 for laboratory confirmed COVID-19 cases for all of China. Modified from *Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)*. 16-24 February 2020. [https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-\(covid-19\)](https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19))

Wednesday, 26 February

A **president**, fearing for his chances to be re-elected, downplays the threat from the coronavirus pandemic, twittering: “Low Ratings Fake News...are doing everything possible to make the Caronavirus [sic] look as bad as possible, including panicking markets, if possible.”

<https://www.bmj.com/content/368/bmj.m941>

Two days later, the same individual invokes magic: “It’s going to disappear. One day, it’s like a miracle, it will disappear.”

P.S. On 28 March, The Guardian would ask why this person
[failed the biggest test of his life.](#)

Friday, 28 February

A quick look at European cases diagnosed outside of Italy from February 24-27 reveals that 31 of 54 people (57%) had recently travelled to **Northern Italy**. Epidemiologists immediately realize that an unusual situation is building up.

Saturday, 7 March

Official data show that **China's exports** plunged 17.2 percent in the first two months of the year.

Sunday, 8 March

The Italian government led by Prime Minister Giuseppe Conte, deserves credit for instauring the first European lockdown, just two and a half weeks after the first autoctone Italian COVID-19 case was detected. First, strict quarantine measures are imposed on 16 million people in the state of Lombardy and 14 other areas in the north. Two days later, Conte would extend these to the entire country of 60 million people, declaring the Italian territory a "security zone". All people are told to stay at home unless they need to go out for "valid work or family reasons". Schools are closed.

Monday, 9 March

A president on Twitter: "So last year 37,000 Americans died from the common Flu. It averages between 27,000 and 70,000 per year. Nothing is shut down, life & the economy go on. At this moment there are 546 confirmed cases of Coronavirus, with 22 deaths. Think about that!" ([The Guardian](#))

Iran releases 70,000 prisoners because of the coronavirus outbreak in the country.

Tuesday, 10 March

Xi Jinping tours the city of **Wuhan** and claims a provisional victory in the battle against COVID-19. The last two of 16 temporary hospitals in the city are shut down.

Wednesday, 11 March

With more than 118,000 COVID-19 cases in 114 countries and 4,291 deaths, WHO DG declares the coronavirus outbreak a pandemic.

All schools in and around **Madrid**, from kindergartens to universities, are closed for two weeks.

Thursday, 12 March

Italy closes all shops except grocery stores and pharmacies.

In **Spain**, 70,000 people in Igualada (Barcelona region) and three other municipalities are quarantined for at least 14 days. This is the first time Spain adopts measures of isolation for entire municipalities.

Emmanuel Macron, the **French** president, announces the closure of nurseries, schools and universities from Monday, 16 March. He declares: “One principle guides us to define our actions, it guides us from the start to anticipate this crisis and then to manage it for several weeks, and it must continue to do so: it is **confidence in science**. It is to **listen to those who know**.” Some of his colleagues should have listened, too.

Friday, 13 March

The prime minister of an **ex-EU country** introduces the notion of ‘herd immunity’ as a solution to repeated future episodes of coronavirus epidemics. The shock treatment: accepting that 60% of the population will contract the virus, thus developing a collective immunity and avoiding future coronavirus epidemics. The figures are dire. With a little over 66 million inhabitants, some 40 million people would be infected, 4 to 6 million would become seriously ill, and 2 million would require intensive care. Around 400,000 Britons would die. The prime minister projects that “many more families are going to lose loved ones before their time.”

P.S. Five weeks later, The Guardian would still ask, [“How did Britain get its coronavirus response so wrong?”](#)

Saturday, 14 March

The **Spanish** government puts the whole country into lockdown, telling all people to stay home. Exceptions include buying food or medical supplies, going to hospital, going to work or other emergencies.

The **French** government announces the closure of all “non-essential” public places (bars, restaurants, cafes, cinemas, nightclubs) after midnight. Only food stores, pharmacies, banks, tobacconists, and petrol stations may remain open.

Sunday, 15 March

France calls 47 million voters to the poll. Both government and opposition leaders seem to be in favor of maintaining the municipal elections. Is this a textbook example of unacceptable interference of party politics with the sound management of a deadly epidemic? Future historians will have to investigate.

Monday, 16 March

Ferguson et al. publish a new modelling study on likely UK and US outcomes during the COVID-19 pandemic. In the (unlikely) absence of any control measures or spontaneous changes in individual behaviour, the authors expect a peak in mortality (daily deaths) to occur after approximately 3 months. This would result in 81% of the US population, about 264 million people, contracting the disease. Of those, 2.2 million would die, including 4% to 8% of Americans over age 70. More important, by the second week in April, the demand for critical care beds would be 30 times greater than supply.

The model then analyzes two approaches: mitigation and suppression. In the mitigation scenario, SARS-CoV-2 continues to spread at a slow rate, avoiding a breakdown of hospital systems. In the suppression scenario, extreme social distancing measures and home quarantines would stop the spread of the virus. The study also offers an outlook at the time when strict “Stay at home” measures are lifted. The perspective is grim: the epidemic would bounce back.

France imposes strict confinement measures.

Tuesday, 17 March

Seven million people across the **San Francisco Bay Area** are instructed to “shelter in place” and are prohibited from leaving their homes except for “essential activities” (purchasing food, medicine, and other necessities). Most businesses are closed. The exceptions: grocery stores, pharmacies, restaurants (for takeout and delivery only), hospitals, gas stations, banks.

Thursday, 19 March

For the first time since the beginning of the coronavirus outbreak, there have been **no new cases in Wuhan** and in the Hubei province.

Californian Governor Gavin Newsom orders the entire population of **California** (40 million people) to “stay at home”. Residents can only leave their homes to meet basic needs like buying food, going to the pharmacy or to the doctor, visiting relatives, exercising.

Friday, 20 March

Italy reports 6,000 new cases and 627 deaths in 24 hours.

In **Spain**, the confinement due to the coronavirus reduces crime by 50%.

China reports no new local coronavirus cases for three consecutive days. Restrictions are eased, **normal life resumes**. The entire world now looks at China. Will the virus spread again?

The state of **New York**, now the center of the U.S. epidemic (population: 20 million), declares a general lockdown. Only essential businesses (grocers, restaurants with takeout or delivery, pharmacies, and laundromats) will remain open. Liquor stores? Essential business!

Sunday, 22 March

Byung-Chul Han publishes *La emergencia viral y el mundo de mañana* (El País): “Asian countries are managing this crisis better than the West. While there you work with data and masks, here you react late and borders are opened.”

Monday, 23 March

Finally, too late for many observers, the UK puts in place containment measures. They are less strict than those in Italy, Spain and France.

German Chancellor Angela Merkel self-quarantines after coming into contact with a person who tested positive for coronavirus.

Tuesday, 24 March

Off all reported cases in Spain, 12% are among health care workers.

The Tokyo Olympics are postponed until 2021.

India orders a nationwide lockdown. Globally, three billion people are now in lockdown.

Wednesday, 25 March

After weeks of stringent containment measures, Chinese authorities lift travel restrictions in Hubei province. In order to travel, residents will need the “Green Code” provided by a monitoring system that uses the AliPay app.

A 16-year-old girl dies in the south of Paris from COVID-19. The girl had no previous illnesses.

Thursday, 26 March

America First: the US is now the country with most known coronavirus cases in the world.

For fear of reactivating the epidemic, China bans most foreigners from entering the country.

Friday, 27 March

The [Prime Minister](#) and the Ministre of Health of an ex-EU country tests positive for coronavirus.

The Lancet publishes *COVID-19 and the NHS—"a national scandal"*.

A paper by [McMichael et al.](#) describes a 33% case fatality rate for SARS-CoV-2 infected residents of a long-term care facility in King County, Washington, US.

Sunday, 29 March

[The Guardian](#) and the [Boston Globe](#) ask who might have blood on their hands in the current pandemic. The evolution of the US epidemic is being described as the [worst intelligence failure in US history](#).

Monday, 30 March

[Flaxman S et al.](#) from the Imperial College COVID-19 Response Team publish new data on the possibly true number of infected people in **11 European countries**. Their model suggests that as of 28 March, in Italy and Spain, 5.9 million and 7 million people could have been infected, respectively (see [Table](#) online). Germany, Austria, Denmark and Norway would have the lowest infection rates (proportion of the population infected). These data suggest that the **mortality of COVID-19 infection** in Italy could be in the range of 0.4% (0.16%-1.2%).

Moscow and **Lagos** (21 million inhabitants) go into lockdown.

The COVID-19 crisis causes some **East European political leaders** to consider legislation giving them extraordinary powers. In one case, a law was passed extending a state of emergency indefinitely.

SARS-CoV-2 is spreading aboard the aircraft carrier USS *Theodore Roosevelt*. The ship's commanding officer, Captain Brett Crozier, sends an email to three admirals in his chain of command, recommending that he be given permission to evacuate all non-essential sailors, to quarantine known COVID-19 cases, and sanitize the ship. "We are not at war. [Sailors do not need to die](#)," writes Crozier in his four-page memo. The letter leaks to the media and generates several headlines. Three days later, 2 April, Captain Crozier is sacked.

Later, testing of 94% of the crew of roughly 4,800 people would reveal around 600 sailors infected, a majority of whom, around 350, were asymptomatic.

April

Wednesday, 1 April

The United Nations chief warns that the coronavirus pandemic presents the world's "worst crisis" since World War II.

Thursday, 2 April

Worldwide more than one million cases are reported. The true number is probably much higher (see the [Flaxman paper](#) on 30 March).

European newspapers run articles about why Germany has so few deaths from COVID-19.

Friday, 3 April

Some economists warn that [unemployment](#) could surpass the levels reached during the [Great Depression in the 1930s](#). The good news: almost all governments rate saving tens or hundreds of thousands of lives higher than avoiding a massive economic recession. Has humanity become more human?

Le Monde, the most influential French newspaper, points to a more [mundane side effect](#) of the epidemic. As hairdressers are forbidden to work, colors and cuts will degrade. The newspaper predicts that "after two months, 90% of blondes will have disappeared from the face of the Earth".

Saturday, 4 April

In Europe, there are signs of hope. In Italy, the number of people treated in intensive care units decreases for the first time since the beginning of the epidemic.

In France, 6,800 patients are treated in intensive care units. More than 500 of these have been evacuated to hospitals from epidemic hotspots like Alsace and the Greater Paris area to regions with fewer COVID-19 cases. Specially adapted TGV high-speed trains and aircraft have been employed.

Lombardy decides that as of Sunday 5 April, people must wear masks or scarves. Supermarkets must provide gloves and hydroalcoholic gel to their customers.

An Italian politician, less penetrable to scientific reasoning on a par with some of his colleagues in the US and Brazil, asks for churches to be open on Easter (12 April), declaring that "science alone is not enough: the good God is also needed". *Heureux les simples d'esprit*, as the French would say.

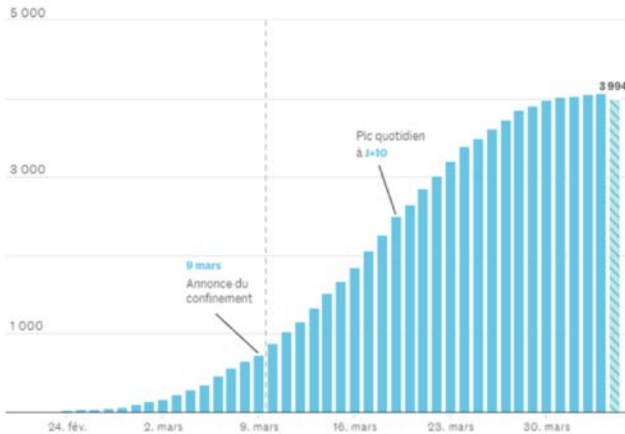


Figure 2. Patients treated in intensive care units in Italy. For the first time since the beginning of the epidemic, the number decreases on 4 April.

Source: [Le Monde](#)

Sunday, 5 April

The US surgeon general warns the country that it will face a “[Pearl Harbor moment](#)” in the next week.

US is the new epicenter of the COVID-19 epidemic. By the time of this writing (5 April), more than 300,000 cases and almost 10,000 deaths were reported. Almost half were reported from New York and New Jersey.

Tuesday, 7 April

Air quality improves over Italy, the UK and Germany, with falling levels of carbon dioxide and nitrogen dioxide. Will a retrospective analysis of the current lockdown reveal fewer cases of asthma, heart attacks and lung disease?

Wednesday, 8 April

Japan declares a state of emergency, Singapore orders a partial lockdown.

In Wuhan people are allowed to travel for the first time since the city was sealed off 76 days ago.

The Guardian publishes a well-documented timeline: “[Coronavirus: 100 days that changed the world.](#)”

Thursday, 9 April

EU finance ministers agree to a common emergency plan to limit the impact of the coronavirus pandemic on the European economy. The Eurogroup reaches a deal on a [response plan worth more than €500 billion](#) for countries hit hardest by the epidemic.

Passenger air travel has decreased by up to 95%. How many of the 700 airlines will [survive](#) the next few months? Will the current interruption of global air travel [shape our future travel behaviors](#)?

The epidemic is devastating the US economy. More than 16 million Americans have submitted unemployment claims in the past three weeks.

Friday, 10 April

COVID-19 treatment for one dollar a day? [British, American and Australian researchers](#) estimate that it could indeed cost only between 1 and 29 dollars per treatment and per patient.

Message from your mobile phone: “You have been in contact with someone positive for coronavirus.” Google and Apple announce that they are **building a coronavirus tracking system into iOS and Android**. The joint effort would enable the use of Bluetooth technology to establish a voluntary contact-tracing network. Official apps from public health authorities would get extensive access to data kept on phones that have been in close proximity with each other (George Orwell is turning over in his grave). If users report that they’ve been diagnosed with COVID-19, the system would alert people if they were in close contact with the infected person.

Spain discovers *COVID Reference*. Within 24 hours, more than 15,000 people download the [PDF of the Spanish edition](#). The only explanation: a huge media platform displayed the link of our book. Does anyone know who did it?

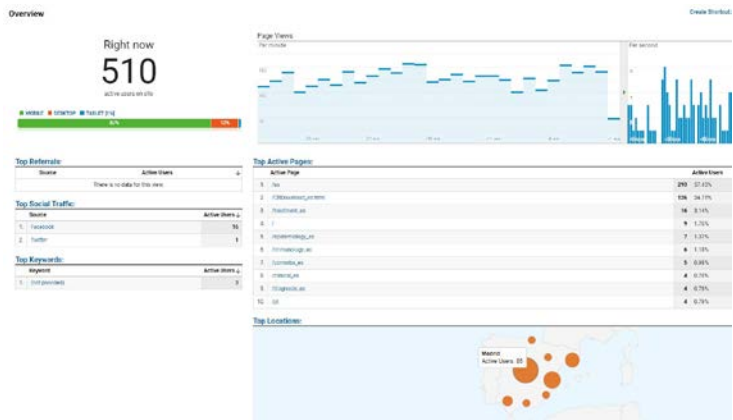


Figure 3. Google Analytics data for www.CovidReference.com on 10 April. At one moment, more than 500 people, mostly from Spain, were visiting the website simultaneously.

Saturday, 11 April

More than **400 of 700 long-term care facilities** (EHPAD in French, *Etablissement d'Hébergement pour Personnes Agées Dépendantes*) in the greater Paris region (pop. – 10 million) have COVID-19 cases.

In Italy, **110 doctors** and about 30 other hospital workers have died from COVID-19, half of them nurses.

Sunday, 12 April

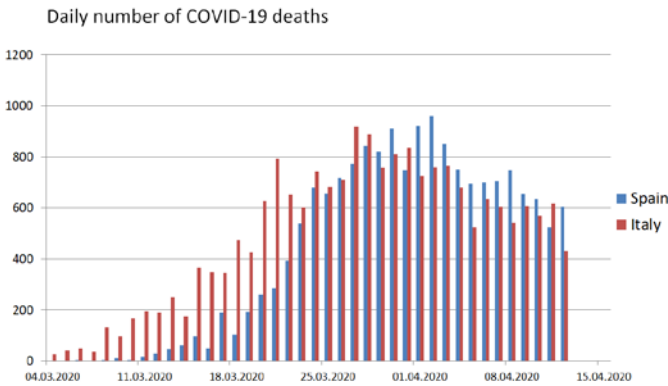


Figure 4. Daily number of COVID-19 deaths in Italy (red) and Spain (blue).

Easter 2020. Italy reports 361 new deaths, the lowest number in 25 days while Spain reports 603 deaths, down more than 30% from a high 10 days before.

The United Kingdom records its highest daily death toll of almost 1,000. The number of reported COVID-19-linked fatalities now exceeds 10,000. As in many other countries, the true numbers may be slightly higher due to underreporting of [people dying in care homes](#).

The number of COVID-19-related deaths in the United States passes 22,000, while the number of cases tops 500,000. In New York there are signs that the pandemic could be nearing its peak.

Monday, 13 April

The COVID-19 pandemic exposes **bad governance**, not only in Brazil. The French newspaper *Le Monde* reveals the ingredients: denial of reality, search for a scapegoat, omnipresence in the media, eviction of discordant voices, political approach, isolationism and short-term vision in the face of the greatest health challenge in recent decades. [The culprit?](#)

Emmanuel Macron announces a **month-long extension to France's lockdown**. Only on Monday, May 11, nurseries, primary and high schools would gradually reopen, but not higher education. Cafés, restaurants, hotels, cinemas and other leisure activities would continue to remain closed after May 11.

Tuesday, 14 April

Austria is the first European country to **relax lockdown measures**. It opens up car and bicycle workshops, car washes, shops for building materials, iron and wood, DIY and garden centers (regardless of size) as well as smaller dealers with a customer area under 400 square meters. These shops must ensure that there is only one customer per 20 square meters. In Vienna alone, 4,600 shops are allowed to open today. Opening times are limited to 7.40 a.m. to 7 p.m. The roadmap for the coming weeks and months:

- 1 May: All stores, shopping malls and hairdressers reopen (see also the April 3 entry, page 447).
- 15 May: Other services such as restaurants and hotels remain closed at least until mid-May.
- 15 May or later: Possible re-opening of classes in schools.

- July: possible – but improbable – organization of events of all sorts (sport, music, theater, cinema etc.).

There is a general obligation to wear a mask when shopping and on public transport.

The International Monetary Fund (IMF) forecasts a **contraction of 3% of the planet's GDP in 2020**. The possibility of an even more brutal fall in 2021 is not excluded. The possibly worst economic downturn since the Great Depression in 1929 will not spare any continent. In a recession like no other in peacetime for nearly a century, the countries of the eurozone, the United Kingdom and the United States might see a contraction in activity of between 5.9% and 7.5%. China's economy is expected to grow by about 1%.

US: The CDC ([Centers for Disease Control and Prevention](#)) reports that more than 9,000 health care workers contracted COVID-19 as and at least 27 died. The median age was 42 years, and 73% were female. Deaths most frequently occurred in HCP aged ≥ 65 years.

Wednesday, 15 April

[Philip Anfinrud and Valentyn Stadnytsky](#) from the National Institutes of Health, Bethesda, report a laser light-scattering experiment in which speech-generated droplets and their trajectories were visualized. They find that when a test person says, “stay healthy,” numerous droplets ranging from 20 to 500 μm are generated. When the same phrase is uttered three times through a slightly damp washcloth over the speaker's mouth, the flash (droplet) count remains close to the background level. The video supports the recommendation of wearing face masks in public. The authors also found that the number of flashes (droplets) increased with the loudness of speech. The new message for billions of people caught in the COVID-19 epidemic: lower your voice!

Friday, 17 April

Luiz Inácio Lula da Silva, the former Brazilian president says that the current president is leading Brazil to “the slaughterhouse” with his irresponsible handling of coronavirus. In an [interview with The Guardian](#), Lula says that Brazil's “troglydyte” leader risks repeating the devastating scenes playing out in Ecuador where families have to dump their loved ones' corpses in the streets.

On the **French aircraft carrier Charles-de-Gaulle**, a massive epidemic is. Among the 1760 sailors, 1,046 (59%) are positive for SARS-CoV-2, 500 (28%)

present symptoms, 24 (1.3%) sailors are hospitalized, 8 on oxygen therapy and one in intensive care.

Saturday, 18 April

Chancellor Angela Merkel makes a television speech, her first in over 14 years in office. She describes the coronavirus crisis “as the greatest challenge since the Second World War” and exhorts the Germans: “It is serious. Take it seriously.”

Care England, Britain’s largest representative body for care homes, suggests that up to 7,500 residents may have died of COVID-19. This would be higher than the 1,400 deaths estimated by the government.

In *Catalunya alone*, some 6,615 hospital professionals and another 5,934 in old age care homes are also suspected of having or been diagnosed with COVID-19.

Sunday, 19 April

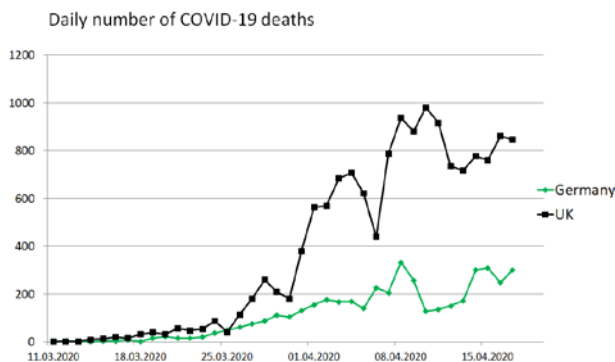


Figure 5. Daily number of COVID-19 deaths in Germany (green) and the United Kingdom (black).

Air traffic in Europe has plummeted more than 95% as nicely shown by this YouTube video by The Guardian: <https://www.youtube.com/watch?v=l0VP2o3c4Gw>

Monday, 20 April

For the first time in history, the West Texas Intermediate (WTI), the benchmark price for US oil, drops below \$0. On certain specific contracts, it plunged down to minus 37 US dollars (-34 euros). After nearly two months of continu-

ous collapse of the oil market, this paradoxical situation is the result of the COVID-19 pandemic which caused demand to fall by 30%. As oil wells continue to produce, there is no place to store the oil and investors are ready to pay to get rid of it.

Germany's [Oktoberfest is cancelled](#). The iconic beer festival, colloquially known as *Die Wiesn* or "the meadow", attracts around 6 million visitors from around the world. It runs for more than two weeks (September/October) in packed tents with long wooden tables, where people celebrate traditional food, dancing, beer and clothing. The loss for the city of Munich is estimated to be around one billion euros.

Tuesday, 21 April

The Spanish newspaper El País publishes an [intelligible overview](#) of the battle between SARS-CoV-2 and the human body: "Así es la lucha entre el sistema inmune y el coronavirus." ¡Fantástico!

[Cancer Research UK](#) reports that every week, 2,300 people with cancer symptoms are no longer examined. Screening examinations for breast and uterine cancer of over 200,000 women per week have been cancelled. According to [The British Heart Foundation](#), 50 percent fewer people suspected of having a heart attack attended hospital emergency rooms in March. A 50% drop would be "equivalent to approximately 5000 of the expected people every month, or more than 1100 people every week, with possible heart attack symptoms not being seen in emergency departments." Will we discover a hidden epidemic of COVID-19-related morbidity and mortality with millions of people dying not from coronavirus, but from other, actually treatable diseases?

Thursday, 23 April

Pandemic hilarity, as a president known for his poor science record stammers speculations about ["injecting"](#) ["disinfectant"](#) to cure COVID-19.

Sunday, 26 April

The city of Wuhan announces that all remaining COVID-19 cases have been discharged from the hospitals.

Monday, 27 April

Are genes determining coronavirus symptoms? After studying 2,633 identical and fraternal twins who were diagnosed with COVID-19, a group from King's College London reports that COVID-19 symptoms appear to be 50% genetic

(fever, diarrhea, delirium and loss of taste and smell)¹⁸. It is as yet unclear whether and to what extent **reported deaths of identical twins** can be attributed to genetic factors.

¹⁸ Williams FMK et al. **Self-reported symptoms of covid-19 including symptoms most predictive of SARS-CoV-2 infection, are heritable**. MedRxiv 27 April (accessed 8 May 2020). Abstract: <https://www.medrxiv.org/content/10.1101/2020.04.22.20072124v2>

May

Friday, 1 May

A new SARS-CoV-2 test could be able to identify virus carriers before they are infectious, according to a report by [The Guardian](#). The blood-based test would be able to detect the virus's presence as early as 24 hours after infection – before people show symptoms and several days before a carrier is considered capable of spreading it to other people.

Sunday 3 May

Roche gets US Food and Drug Administration emergency use approval for its antibody test, [Elecsys](#) Anti-SARS-CoV-2, which has a specificity rate of about 99.8% and a sensitivity rate of 100%.

Monday, 4 May

Italy is cautiously easing lockdown measures. People can go jogging but may not go to the beach; they may surf but now swim; and they can visit 6th grade relatives, but not friends, lovers or mistresses.

A French hospital that retested old samples from pneumonia patients discovers that it treated a man with the coronavirus [as early as 27 December](#), a month before the French government confirmed its first cases.

Researchers from Bonn University, Germany, report a [sero-epidemiological study](#) of 919 people from Gangelt, a small German town which was exposed to a super-spreading event (carnival festivities). 15.5% were infected, with an estimated infection fatality rate of 0.36%. 22% of infected individuals were asymptomatic.

Tuesday, 5 May

Neil Ferguson, epidemiologist at the Imperial College, resigns his post as member of the British government's Scientific Advisory Group for Emergencies (SAGE) over an "error of judgement". A newspaper had reported that he did not respect the rules of confinement (which he himself had contributed to establishing!) by receiving at least twice a 38-year-old woman at his home.

Anthony Fauci, the director of the United States National Institute of Allergy and Infectious Diseases, says that there is no scientific evidence to back the

theory that the coronavirus was made in a Chinese laboratory or leaked from a laboratory after being brought in from the wild ([CGTN](#)).

Wednesday, 6 May

The official COVID-19 death toll in the UK exceeds 30,000.

Thursday, 7 May

According to data released by the US Department of Labor, more than 33 million Americans have filed for initial jobless claims. This corresponds roughly to 21% of the March labor force.

Only 15 countries in the world have not officially reported a case of COVID-19 to WHO, namely: North Korea, Turkmenistan, Kiribati, Marshall Islands, Micronesia, Samoa, Solomon Island, Tonga, Tuvalu, Vanuatu, Cook Island, Nauru, Niue, Palau and Lesotho. (We know North Korea is cheating, and Turkmenistan and Lesotho cannot deny for long... It's a true pandemic!)

According to figures by the [Office of National Statistics](#), black people are more than four times more likely to die from COVID-19 than white people.

Friday, 8 May 2020

After pipedreams (German: Hirngespinnste; French: élucubrations; Italian: visioni; Spanish: fantasías) about hydroxychloroquine and injecting disinfectants, today is the day where COVID-19 will “go away without vaccine”. The sad developments of the coronavirus pandemic have now accumulated sufficient evidence that the individual doesn't believe himself what he is saying. The carefully timed and well-orchestrated ungrammatical utterings just obey one supreme life mission: continue staying in the news. Alas, there is an even more tragic aspect to the drama: Why on Earth do the world's media insist on talking about this individual? Why can't we read the news without seeing his face every single day? Why couldn't we simply *totschweigen* him? (*Totschweigen* is a superbly descriptive German verb: 1. tot dead; 2. schweigen to be silent; 3. totsichweigen make someone dead silent – English: to hush up; French: passer sous silence; Italian: fare come se non esistesse; Portuguese: não falar em alguém.)

Today, we make a funereal promise: we'll never talk about the individual again, not even on the day he dies.

Sunday, 10 May

Italians are looking on aghast at the UK's coronavirus response, says [The Guardian](#). Is it really no accident that Britain and America are the world's [biggest coronavirus losers](#)?

Everything you always wanted to know about false negatives and false positives* (*but were afraid to ask) is now summarized in [10 steps to understand COVID-19 antibodies](#). The colors will help you memorize true and false negatives and positives.

Spain's best newspaper El País publishes '[ccu ccg ccg gca - The 12 letters that changed the world.](#)' (if you read Spanish, take a look.)

Monday, 11 May

France eases lockdown restrictions among a sense of uncertainty. The newspaper [Le Monde reports](#) that according to official figures 8,674 new positive tests for SARS-CoV-2 were registered between May 1 and 9. Epidemiologist Daniel Lévy-Bruhl, head of the respiratory infections unit of Santé Publique France (Public Health France) estimates that the real figures are probably twice or three times as high (3,000 to 4,000 new infections each day) – despite barrier gestures, social distancing and general confinement.

Tuesday, 12 May

The MMWR publish a report about a [high SARS-CoV-2 attack rate following exposure at a choir practice](#).

Wednesday, 13 May

There is evidence that **China** is **censoring COVID Reference**. Google Analytics data of two dozen websites, both medical ([Amedeo](#), [Free Medical Journals](#), [FreeBooks4Doctors](#)) and non-medical ([TheWordBrain](#), [Ear2Memory](#), [GigaSardinian](#), [GigaMartinique](#), [SardoXSardi](#), [Polish Yiddish](#) and [ItalianWithElisa](#), among others) show that by number of visitors, China was always among the *Top 10 countries*, generating between 3.3% and 14.8% of website traffic (see <https://covidreference.com/censorship>).

Not so with COVID Reference. Six weeks after the launch of COVID Reference, China is 27th, after Paraguay, accounting for 0.39% of global traffic. Is someone standing on the data line between COVID Reference and China (Figure 6)?

25.	 Costa Rica	790 (0.42%)
26.	 Paraguay	744 (0.40%)
27.	 China	727 (0.39%)
28.	 Netherlands	716 (0.38%)
29.	 Russia	613 (0.33%)

Figure 6. Google Analytics data for www.CovidReference.com on 13 May. Six weeks after the launch of COVID Reference, China is 27th, after Paraguay and right before the Netherlands and Russia.

Friday, 15 May

In a memorable [blog entry for the British Medical Journal](#), Paul Garner, professor of infectious diseases at Liverpool School of Tropical Medicine, discusses his COVID-19 experience as having “been through a roller coaster of ill health, extreme emotions, and utter exhaustion”.

A [video experiment](#) using black light and a fluorescent substance demonstrates how quickly germs can be spread in environments such as restaurant buffets and cruise ships: www.youtube.com/watch?v=kGQEuuv9R6E.

Saturday, 16 May

A new highly transmissible and potentially deadly virus is detected in Germany: **SADS**, Severe Acute Dementia Syndrome. The new syndrome manifests as an irrepressible desire to ignore the danger of COVID-19. In several German cities, an improbable alliance takes to the streets – left- and right-wing extremists, antisemites, conspiracy theorists and anti-vaxxers –, claiming the right to live and to die without social distancing and face masks. The German Government immediately informs WHO.

Monday, 18 May

Merkel and Macron announce a 500,000 million euro aid plan for the reconstruction of Europe ([El País](#)).

Moderna announces that its experimental vaccine mRNA-1273 has generated antibodies in eight healthy volunteers ages 18 to 55. The levels of neutralizing antibodies matched or exceeded the levels found in patients who had recovered from SARS-CoV-2 infection ([The Guardian](#)).

Wednesday, 20 May

After an outbreak of coronavirus, Chinese authorities seal off the city of Shulan, a city of 700,000 close to Russian border, imposing measures similar to those used in Wuhan ([The Guardian](#)).

Google and Apple release their Exposure Notification System to notify users of coronavirus exposure: <https://www.google.com/covid19/exposurenotifications>.

We discover a website which shows where infected people in Hong Kong are at all times: <https://chp-dashboard.geodata.gov.hk/covid-19/en.html> (Figure 7). There is no doubt that the tighter you control the infected, the less restriction you have to impose on the uninfected. In Europe, strict measures such as those adopted in Hong Kong and South Korea are currently not compatible with existing legislation about privacy.

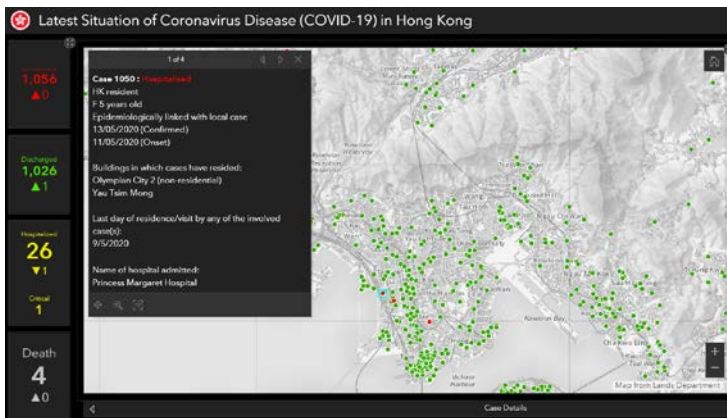


Figure 7. Screenshot of the "Latest Situation of Coronavirus Disease (COVID-19) in Hong Kong", <https://chp-dashboard.geodata.gov.hk/covid-19/en.html>.

Thursday, 21 May

The Centers for Disease Control and Prevention (CDC) informs that rats rely on the food and waste generated by restaurants and other commercial establishments, the closures of which have led to food shortage among rodents, especially in dense commercial areas. CDC warns of [unusual or aggressive rodent behavior](#).

Will SARS-CoV-2 seal the fate of the Airbus A380? Air France chooses to end the operations of the aircraft, judged to be too expensive, too polluting and not profitable enough ([Le Monde](#)).

Friday, 22 May

Zhu et al. publish *Safety, Tolerability, and Immunogenicity of a Recombinant Adenovirus type-5 Vectored COVID-19 Vaccine*.

Fafi-Kremer 2020 et al. pre-publish *Serologic responses to SARS-CoV-2 infection among hospital staff with mild disease in eastern France*, reporting that neutralizing antibodies against SARS-CoV-2 were detected in virtually all hospital staff (n=160) sampled from 13 days after the onset of COVID-19 symptoms (see also [Le Monde](#)).

Saturday, 23 May

In Lower Saxony, Germany, 50 people are in quarantine after an outbreak in a restaurant ([Der Spiegel](#)).

In Frankfurt, Germany, authorities report more than 40 people infected with SARS-CoV-2 after a religious service ([Der Spiegel](#)).

Wednesday, 27 May

Colombian designers prepare cardboard hospital beds that double as coffins ([The Guardian](#)).

Andrzej Krauze publishes a [cartoon](#) on the fallout from the COVID-19 pandemic.

Sunday, 31 May

More than 50 million people across the US could go hungry without help from food banks or other aid ([Feeding America](#)).

June

Wednesday, 3 June

In the hope of saving its tourist industry, Italy reopens its borders.

Tuesday, 4 June

The Lancet *makes one of the biggest retractions in modern history* (The Guardian).

Friday, 5 June

The chief investigators of the RECOVERY trial report that there is **no clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19**.

Saturday, 6 June

The Guardian reports that **nearly 600 US health workers have died of COVID-19**.

Sunday, 7 June

Three super-spreading events in an office, a restaurant and a bus show how easily SARS-CoV-2 can be spread over distances of more than 1 meter. The feature by *El País* is worth taking a look, even if you don't understand Spanish: <https://elpais.com/ciencia/2020-06-06/radiografia-de-tres-brotes-asi-se-contagiaron-y-asi-podemos-evitarlo.html>.

Monday, 8 June

Attending a sporting event, concert or play? Attending a wedding or a funeral? Stopping routinely wearing a face covering? Attending a church or other religious service? Hugging or shaking hands when greeting a friend? Going out with someone you don't know well? When asked by The New York Times when they would expect to resume these activities of daily life, 42% to 64% of epidemiologists and infectious disease specialists answered they would prefer waiting a year before doing it again. The enquiry by Margot Sanger-Katz, Claire Cain Miller and Quoc Trung Bui: **When 511 epidemiologists expect to fly, hug and do 18 other everyday activities again**.

It becomes increasingly clear that not all patients recover fully from SARS-CoV-2 infection. See **'It feels endless': four women struggling to recover from Covid-19**. (If you read Spanish, check also *Los últimos de la UCI*).

Dozens of [new infections reported in Kabukicho](#), a district of more than 4,000 bars, restaurants and commercial sex establishments in Tokyo.

Tuesday, 9 June

New Zealand returns [back to pre-COVID-19 life](#).

In Brazil, “poverty, poor access to health services and overcrowding all play a part in a disproportionate number of deaths”, reports [The Guardian](#). Coronavirus death rates expose Brazil’s deep racial inequalities.

Wednesday, 10 June

The Guardian publishes an analysis of the [Surgisphere scandal](#) (the retracted paper about hydroxychloroquine trial).

NIAID Director Anthony Fauci says the [coronavirus pandemic is far from over](#).

The OECD says [Britain](#) will top the developing world’s recession league table.

[British theatre might go out of business](#).

Thursday, 11 June

India, Mexico, Russia, Iran and Pakistan decide to [end lockdowns](#).

Neil Ferguson, a former scientific adviser to the British government, says earlier restrictions [could have halved the death toll](#).

If you read Spanish: *Las mascarillas, claves para evitar una segunda oleada de la pandemia* (El País).

Friday, 12 June

[Beijing reimposes lockdown measures](#) after a new COVID-19 outbreak around the wholesale market of Xinfadi (北京新发地水果批发市场).

Northwestern Memorial Hospital in Chicago announces that a young woman in her 20s whose lungs were destroyed by COVID-19 [received a double lung transplant](#).

If you read French: *Coronavirus – au cœur de la bataille immunitaire contre le virus*.

Saturday, 13 June

What have Venice, Amsterdam and Barcelona in common? Before the COVID-19 pandemic they were overrun by tourists. Tourism certainly contributes to the wealth of these cities, but the vast majority of the populations – all those who are not directly or indirectly employed in mass tourism – receive no

benefits from millions of people transiting their neighborhood. The weekend of 13/14 June, just before the reopening of the Schengen area (see 15 June entry), is therefore a unique opportunity for people in hundreds of small and big charming cities throughout Europe. They enjoy the place where they live with those who were born there or chose to live there – like 10, 20 or 30 years ago, before the beginning of the tourist pandemic.

According to figures from the British Office for National Statistics (ONS), people living in more deprived areas are twice as likely to die from coronavirus (ONS | [The Guardian](#)).

Most Europeans now [trust their leaders generally a little](#) less than when the crisis began.

Malta's abortion taboo leaves [women in despair](#).

Sunday, 14 June

Lancet editor Richard Horton describes the management of the outbreak as '[the greatest science policy failure of a generation](#)'.

Immunologist Scott Canna and rheumatologist Rachel Tattersall publish a 23-minute audio about [cytokine storms](#).

A study by Ben Etheridge and Lisa Spantig shows that one third of women suffered from [lockdown loneliness](#).

Thailand, Malaysia, Vietnam... some countries [managed to keep COVID at bay](#).

When should we send children back to school? Here is what [132 epidemiologists](#) would be inclined to do.

Monday, 15 June

Mauro Giacca of King's College London: "[Covid-19 can result in complete disruption of the lung architecture](#)."

With a few exceptions, all borders in the [European Schengen area](#) are open again for free travel of European citizens. The [Balearic Islands open to 11,000 German tourists](#).

Every stairway a marathon? There is no standard therapy for patients who have survived a severe corona infection. For many survivors, the way back to a normal life begins in rehabilitation clinics. If you read German, [read this](#).

Tuesday, 16 June

Results from the RECOVERY trial: Dexamethasone is the first life-saving coronavirus drug ([Study](#) | [The Guardian](#)).

After hundreds of infections at the Xinfadi market, the Chinese authorities close all schools and call on residents to avoid “non-essential” travel outside of the city. Around thirty residential areas surrounding the market are quarantined. Companies are encouraged to favor teleworking and people can no longer, except in cases of force majeure, leave the capital. Around 67% of domestic flights are canceled. Libraries, museums, art galleries and parks can only operate at 30% of their capacity. Restaurants can no longer accommodate groups. Beijing begins screening tens of thousands of inhabitants, bringing its daily testing capacity to more than 90,000 people.

The U.S. Food and Drug Administration [revokes its emergency use authorization](#) for hydroxychloroquine sulfate and chloroquine phosphate to treat COVID-19.

Coronavirus cases rise in [US prisons](#).

Wednesday, 17 June

Investigations from Nanjing show that turbulence from a toilet bowl can create a large plume that is potentially infectious to a bathroom’s next visitor ([Paper](#) | [The New York Times](#)).

After two women recently arrived from Britain were infected with COVID-19 and allowed to leave quarantine without being tested, New Zealand puts COVID-19 [quarantine in the hands of the military](#).

Thursday, 18 June

The end of tourism? [Christopher de Bellaigue](#) publishes an insightful Guardian *long read* about the devastated global tourism industry. One key paragraph: “Tourism is an unusual industry in that the assets it monetizes – a view, a reef, a cathedral – do not belong to it. The world’s dominant cruise companies (...) pay little towards the upkeep of the public goods they live off. By incorporating themselves in overseas tax havens with benign environmental and labor laws – respectively Panama, Liberia and Bermuda – cruising’s big three, which account for three-quarters of the industry, get to enjoy low taxes and avoid much irksome regulation, while polluting the air and sea, eroding coastlines and pouring tens of millions of people into picturesque ports of call that often cannot cope with them.”

Eric Rubin and Lindsey Baden discuss [SARS-CoV-2 transmission](#) in a 20-minute audio by the New England Journal of Medicine.

A 13-day-old baby becomes one of the [UK’s youngest victims](#).

Antibodies may fade quickly in asymptomatic people ([Nature](#) | [The New York Times](#)).

Again, meat processing plants are proving to be ideal transmission settings. In the German town of Gütersloh, North Rhine-Westphalia, 657 employees test positive for SARS-CoV-2.

Richard Horton publishes *The COVID-19 Catastrophe: What's Gone Wrong and How to Stop It Happening Again*. "The book returns again and again to the catastrophe in both the United Kingdom and the United States. It is haunted by the question: how did two of the richest, most powerful and most scientifically advanced countries in the world get it so wrong, and cause such ongoing pain for their citizens?" ([Nature](#))

Friday, 19 June

Beijing residents react with [frustration and anxiety](#) after finding almost 200 new cases of coronavirus.

A study by the Italian Istituto Superiore di Sanità detects SARS-CoV-2 RNA in wastewater samples collected in [Milan and Turin on 18 December 2019](#).

Investigations from the University of Sussex describe society as regressing back to the 1950s for many women ([The Guardian](#)).

UK abandons developing its own contact-tracing app and switches to the [alternative design by Google and Apple](#).

Three experts exchange their views on the [risks of travelling by plane](#).

Alexandra Villarreal describes a [new American way of life](#): some Americans return to bars, dining and beaches, others shy away, concerned that the virus is still raging.

Sunday, 20 June

Spain plunges into the so-called [new normal](#) after 98 days of COVID-19 state-of-alarm.

The coronavirus outbreak in the German meat processing plant [Tönnies](#) near [Gütersloh](#) continues. By midday, 1,029 employees test positive and 2,098 negative for SARS-CoV-2. Nineteen people, almost all employees of Tönnies, are being treated for COVID-19. Six of them are in intensive care, two patients are ventilated ([DIE ZEIT](#)).

Those who might be tempted to attend a political rally should read the summary of COVID Reference's [Transmission](#) chapter:

1. It appears that a high percentage (as high as 80%?) of secondary transmissions could be caused by a small fraction of infectious individuals (as low as 10%?; [Endo 2020](#)); if this is the case, then the more people are grouped together, the higher the probability that a **superspreader** is part of the group.
2. It also appears that aerosol transmission might play an important role in SARS-CoV-2 transmission ([Prather 2020](#)); if this is the case, then building a wall around this same group of people and putting a ceiling above them further enhances the probability of SARS-CoV-2 infection.
3. It finally appears that shouting and speaking loudly emits thousands of oral fluid droplets per second which could linger in the air for minutes ([Anfinrud 2020](#), [Stadnytskyi 2020](#), [Chao 2020](#), [Asadi 2019](#)); if this is the case, then creating noise (machines, music) around people grouped in a closed environment would create the perfect setting for a superspreader event.

Stay away from mass gatherings.

Week 26

This week has seen important local outbreaks. The recurring patterns: family celebrations ([Melbourne](#), [Berlin](#), [Lagos](#)) and people living ([Malaga](#), Lisbon), working ([Gütersloh](#), [Tokyo](#), [Huesca](#)) or playing ([Adria Tennis Tour](#)) close together. The next outbreaks are anticipated in [Liverpool](#), [Naples](#) (football celebrations) and some Italian cities ([movida](#)).

On 24 June, the US established a new national SARS-CoV-2 record. In Texas, the number of deaths is expected to increase about two to three weeks from now.

Sunday, 21 June

The number of infections in the Gütersloh (Germany) meat-processing plant exceeds one thousand. Nearly 7,000 employees are quarantined. After repeated outbreaks in the meat industry, The Guardian publishes [Why you should go animal-free: 18 arguments for eating meat debunked](#).

The Spanish authorities increase the purchase of flu vaccines. Immunizations will start as soon as possible and priority will be given to health personnel.

Monday, 22 June

France reopens schools, colleges, kindergartens, cinemas, game rooms and small sports.

In India, 25 [luxury hotels](#) are to be transformed into COVID-19 care centers.

Injectable dexamethasone is more difficult to manufacture than tablets, and could [soon run out](#).

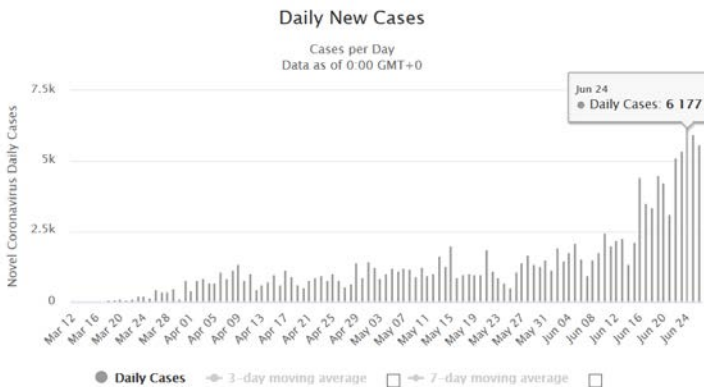
The New York Times publishes [Lessons on Coronavirus Testing From the Adult Film Industry](#).

Wednesday, 24 June

More than 1,500 workers have tested positive in Gütersloh, Germany. The abattoir [cooling systems](#) may have contributed to spreading aerosol droplets laden with coronavirus. The authorities order a [lockdown for 640,000 people](#).

In the US, more than 38,000 cases are detected, a [record](#) since the start of the coronavirus epidemic. The states that lifted containment measures, mainly governed by Republicans, are the most affected.

Daily New Cases in Texas



Source: <https://www.worldometers.info/coronavirus/usa/texas>

Income emerges as a [major predictor of coronavirus infections](#), along with race.

[Tennis player](#) Novak Djokovic tests positive for COVID-19 amid Adria Tour fiasco (dixit Le Monde: Adria Cluster Tour).

The Guardian publishes [The coronavirus backlash: how the pandemic is destroying women's rights](#).

Thursday, 25 June

In young children, SARS-CoV-2 infection is largely asymptomatic or accompanied by few symptoms. Now, two pre-published studies by Fontanet et al. from the Institut Pasteur, Paris, also suggest lower infection rates in a French primary school (6 to 11-years-old) when compared to a high school in [Crépy-en-Valois](#), a small town 60 km northeast of Paris. The studies show that 38% of high school students had antibodies against SARS-CoV-2, but only 8.8% of primary school students in the same town (see following table).

A study of residents in the Alpine ski resort of Ischgl find that [42% have antibodies](#) for the virus.

More than 80 people test positive in an outbreak at a Red Cross center in Málaga.

Tokyo detects new outbreaks of coronavirus in offices, with 55 new cases, its biggest rebound in a month and a half.

	High school students*		Children in primary school**	
Pupils	240	92 (38.3%)	510	45 (8.8%)
Parents	211	24 (11.4%)	641	n.n. (12%)
Close family	127***	13 (10.2%)	119	
Teachers	53	23 (43.4%)	42	3 (7%)
Staff	27	16 (59.3%)	28	1 (3.6%)
Others	3	3 (100%)		
Total	661	171 (25.9%)	1 340	

* Cluster of COVID-19 in northern France, By [Fontanet A, et al.](#)*

** Press report ([Le Monde](#)), incomplete data

*** Siblings

Sokolowska et al. publish *[Immunology of COVID-19: Mechanisms, Clinical Outcome, Diagnostics and Perspectives - A Report of the European Academy of Allergy and Clinical Immunology \(EAACI\)](#)*

The Guardian publishes *[On different planets: how Germany tackled the pandemic, and Britain flailed.](#)*

The New York Times publishes *[How the Virus Won](#)*, analyzing travel patterns, hidden infections and genetic data to show how the epidemic spun out of control.

Liverpool wins Premier League. At the title party, thousands gather on the streets without face masks. Rallies on UK beaches and at street parties in London.

Friday, 26 June

[The Challenges of Safe Reopening](#) – NEJM audio Interview (17:33) with Eric Rubin, Lindsey Baden and Stephen Morrissey.

The Guardian publishes [I'm a viral immunologist. Here's what antibody tests for Covid-19 tell us](#).

The New York Time publishes [How the Coronavirus Short-Circuits the Immune System](#) and [Can Covid Damage the Brain?](#)

Saturday, 27 June

The European Union is preparing to restrict most US residents from visiting the region.

If you read Spanish, read [Más de 100 días arrastrando el coronavirus](#) /by Isabel Valdés.

If you read French, read [Qu'est-ce que le « R0 », le taux de reproduction du virus ?](#) by Gary Dagorn.

If you read Portuguese, read [Durante a Gripe Espanhola, houve uma Liga Anti-Máscara. E tudo piorou.](#)

Week 27

This week witnesses an important resurgence of SARS-CoV-2 infections in the US and India. Meanwhile, Europe which has more or less successfully managed the first wave, is holding its breath: will the economically all-important tourist season smoothly go ahead or will it be grounded by a second COVID wave? For now, smaller outbreaks ([Gütersloh](#), [Leicester](#), [Lleida](#)) are being kept under control. In this context, the opening of closed space where strangers can meet ([bars](#), [brothels](#) and [restaurants](#)) may not be a good idea.

In the meantime, the EU opens its borders to 15 countries, car rental companies expect to lose up to 80%, Gilead imposes a price of about 350 euros per dose for its (weak) anti-SARS-CoV-2 drug, China starts testing a vaccine on military personnel, and [asymptomatic spread continues](#) – why shouldn't it.

Astonishingly, the question of using face masks continues to be debated. While you can probably do without them in low-prevalence areas such as most parts of Southern Italy, you are well-advised to wear them in the US. A

British journalist stated that not wearing face masks in epidemiological hotspots is like driving drunk. Imagine how people feel who are governed by drunkards.

Sunday, 28 June

Ten million official cases and 500,000 COVID-19 deaths.



Source: Johns Hopkins Coronavirus Resource Center.

Monday, 29 June

Chinese CanSino Biologics receives the green light to use a recombinant novel coronavirus vaccine (Ad5-nCoV) within the military.

Tuesday, 30 June

Anthony Fauci warns that a “general anti-science, anti-authority, anti-vaccine feeling” is likely to thwart vaccination efforts ([The Guardian](#)).

India has more than 450,000 confirmed cases, making it the world’s fourth-worst-hit country. Major cities such as Delhi and Mumbai are particularly badly affected ([Nature](#)).

China cuts off more than 400,000 people in [Anxin county](#) to tackle a small COVID-19 cluster ([The Guardian](#)).

The new poor in Italy? Only a small percentage of companies have received promised lockdown help ([The Guardian](#)).

The English city of [Leicester](#) is in local confinement again after 866 new cases are diagnosed in two weeks.

The pharmaceutical company Gilead imposes a price of about 350 euros per dose for its (weak) anti-SARS-CoV-2 drug.

The New England Journal and The Lancet publish three articles ([one](#) | [two](#) | [three](#)) and a [comment](#) about Multisystem Inflammatory Syndrome in Children (MIS-C).

July

Wednesday, 1 July

The New York Times publishes an update on [super-spreaders](#).

Outbreak in Melbourne, Australia. The authorities confine 300,000 people in 30 neighborhoods for a month.

The EU publishes a list of 15 countries from where people should be allowed into the Union. Visitors from the US to remain banned from entering the EU because of the country's rising infection rate.

We discover this YouTube [video by Tang and al.](#) visualizing airflow patterns associated with common, everyday respiratory activities. In this case, talking illustrates rapidly changing airflow patterns exchanged between talkers.

The US [buys up](#) the world stock of remdesivir.

Testing finds cases at US meat-processing plants but officials refuse to release the information ([The Guardian](#)).

According to an article by [Science](#), only 50% of Americans plan to get a COVID-19 vaccine.

Thursday, 2 July

California rolls back the reopening of bars, restaurants and indoor venues ([The Guardian](#)).

Anthony S. Fauci and H. Clifford Lane publish *Four Decades of HIV/AIDS — Much Accomplished, Much to Do*.

Nicholas Kristof publishes *Refusing to Wear a Mask Is Like Driving Drunk*.

Friday, 3 July

Cheng et al. publish *How to Safely Reopen Colleges and Universities During COVID-19: Experiences From Taiwan*.

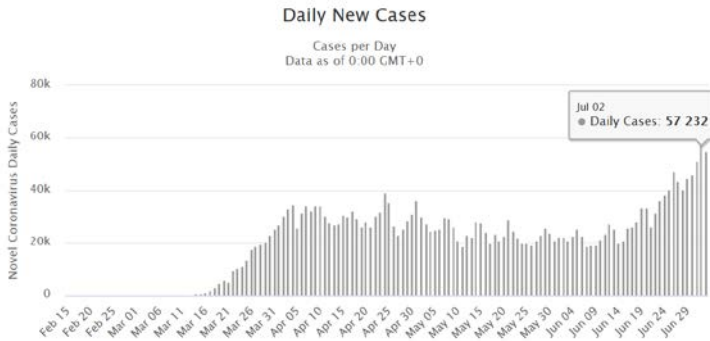
[The Guardian](#) describes the new emergency in Los Angeles.

Saturday, 4 July

The HIV drug lopinavir/ritonavir [fails to reduce mortality](#) in an interim analysis of the Solidarity trial. WHO discontinues both the lopinavir/ritonavir and the hydroxychloroquine treatment arms for COVID-19 ([who.int](#)).

After SARS-CoV-2 outbreaks in fruit companies, a nursing home, a neighborhood community and a hostel for homeless people, Catalonia imposes a [lock-down on 200,000 people](#) around [Lleida](#).

The epidemic is taking off in the US:



Source: <https://www.worldometers.info/coronavirus/country/us/>

Adam Gabbatt publishes [Fourth of July celebrations increase risk of 'superspreader' events](#).

Jesse Wegman publishes [Seriously, Just Wear Your Mask](#).

Michelle Cottle publishes [Florida, America's Pandemic Playground](#).

[Pubs reopen in England](#).

Week 28

Week 28 will be recorded as a watershed in the perception of SARS-CoV-2 transmission risk: yes, the virus is transmitted by fat droplets, and yes, it is also transmitted tiny aerosol particles. If this shift is proven to be right, SARS-CoV-2 may go down in history as the virus that unified the almost century-old dichotomy of droplets vs. aerosol transmission. The merit goes to [Lidia Morawska and Donald K. Milton](#), supported by 237 scientists (see also the comment in [The Guardian](#) and in [The New York Times](#)). In the next days, we will publish an update of our [Transmission chapter](#).

Paterson et al. publish a worrisome article about the neurological complications of COVID-19.

Second waves are leading to partial lockdowns in Australia, Spain, Serbia and Israel while Catalonia and the Balearic Islands order wearing face masks even when the required 1.5-metre social distancing can be observed.

The first wave continues in the US. People in Mexico border towns try to stop Americans from crossing.

Sunday, 5 July

Is it time to address airborne transmission of SARS-CoV-2? It may be high time, say [Lidia Morawska and Donald K Milton](#), supported by other 237 scientists. See also *WHO underplaying risk of airborne spread of Covid-19* (The Guardian), *239 Experts With One Big Claim: The Coronavirus Is Airborne* and *Airborne Coronavirus: What You Should Do Now* (The New York Times).

Spain puts part of Galicia [back into lockdown](#).

Monday, 6 July

Find out how [Anthony Fauci](#), [Elizabeth Connick](#), [Paul A. Volberding](#), [Linda Bell](#), [Barry Bloom](#) and [David Satcher](#) deal with COVID-19 risks in their everyday lives.

Tuesday, 7 July

If you read Spanish, read “La enigmática mutación del coronavirus que ahora domina el planeta” ([El País](#)).

Wednesday, 8 July

COVID-19 fears: People in Mexico border towns try to stop Americans from crossing ([The Guardian](#)).

Paterson et al. publish *The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings*. See also the article published in [The Guardian](#).

[Violence at Belgrade protest](#) over renewed lockdown measures

[Churches at risk](#): SARS-CoV-2 infiltrates Sunday services, church meetings and youth camps. More than 650 cases have been linked to reopened religious facilities.

Second COVID-19 wave in [Israel](#).

Thursday, 9 July

WHO update information about SARS-CoV-2 transmission ([WHO 20200709](#)): “There have been reported outbreaks of COVID-19 in some closed settings, such as restaurants, nightclubs, places of worship or places of work where people may be shouting, talking, or singing. In these outbreaks, aerosol transmission, particularly in these indoor locations where there are crowded

and inadequately ventilated spaces where infected persons spend long periods of time with others, cannot be ruled out.”

Five million Melbourne residents are [locked down again](#) (read also [this article](#)).

Catalonia orders wearing face masks even when the required 1.5-metre social distancing can be observed. The fine for not observing the new rules: [100 euros](#). The Balearic islands is set to [follow Catalonia's lead](#) soon.

The Tokyo authorities pay nightclubs as well as host and hostess bars thousands of dollars if they close for more than 10 days.

Indonesia announces a new cluster of more than 1,000 cases at a military training center in West Java.

Friday, 10 July

[Guardian live](#) (10 July): Bogotá to re-enter strict lockdown.

The Guardian [Global report](#) (10 July).

[Rats](#) torment New York alfresco diners.

Scotland asserts [separateness from England](#).

If you read Spanish, read [El mapa de los brotes de coronavirus: el 40% tiene su origen en encuentros familiares](#).

Saturday, 11 July

The Guardian: [Coronavirus live](#) + [Global report](#).

New outbreak in Spain in L'Hospitalet, the second biggest city in the Barcelona metropolitan area (3.2 million people; [El País](#)).

Over 40 Florida hospitals max out their intensive care unit capacity ([The Guardian](#)).

Rapid serological tests are now available in French pharmacies. The test requires taking a drop of blood by pricking the skin, usually at the fingertip, then putting it in contact with a reagent. The result appears in a few minutes ([Le Monde](#)).

The NY Times publishes [‘I Couldn't Do Anything’: The Virus and an E.R. Doctor's Suicide](#).

If you read Spanish, read the Fauci interview [“La cuestión es que todo el mundo debería llevar mascarilla”](#) ([El País](#)).

Is the governor of the hard-hit Lombardy region (almost 50% of all Italian cases) opening the dance for the second wave in his country? In a bold (suicidal?) move he allows discos to reopen open-air discos. The [Repubblica](#)

newspaper reports that people “filled the slopes of the main Milanese discos without wearing personal protective equipment and without respecting the social distancing.” The countdown has begun.

Week 29

This week, the publication of detailed results of a phase 1, dose-escalation, open-label trial (14 July) reminded us that the race for a vaccine is gaining momentum. More encouraging results from competitor researchers are expected within days.

Meanwhile, the pandemic is gaining momentum, too, with sad records recorded from all over the world. A new area of concern is Europe, where a second wave may be building up (18 July). In contrast to what happened in March, local epidemics seem now to be fueled by the infection of younger people. Wearing face masks may soon be required in many European countries (16 July).

In the US, daily new SARS-CoV-2 cases are on track to go beyond 100,000. As Rudolf Virchow, the great 19th century father of pathological anatomy, liked to say: “An epidemic is a social phenomenon that has some medical aspects.” (Cited by Bernard Henri-Lévy in *Ce virus qui rend fou*, Grasset, June 2020)

Sunday, 12 July

Fourteen renowned doctors (Antoine Pelissolo, Jimmy Mohamed Philippe Amouyel, Francis Berenbaum, Eric Caumes, Robert Cohen, Anne-Claude Crémieux, Gilbert Deray, Vianney Descroix, Philippe Juvin, Axel Kahn, Karine Lacombe, Bruno Megarbane and Christine Rouzioux) demand **“the wearing of a mandatory mask in all enclosed public places”** in order to prevent a second COVID-19 wave ([Le Parisien](#), [Le Monde](#)).

In **Sydney, thousands of pub-goers** have been asked to self-isolate for two weeks after a hotel staff member and three other people became the latest cases in an emerging coronavirus cluster ([The Guardian](#)).

Will COVID-19 help to **cure over-tourism** in the future? Many cities around the world are searching for a new balance. Reflections about the current situation in Paris ([Le Monde](#), [Édition abonnés](#)).

If you read Spanish, read *Los delirios mortales del rey Donald*, by [Paul Krugman](#), and *Jornaleros de la pandemia*, by [Guillermo Abril](#).

Monday, 13 July

California, 40 million people, return to the closure of all indoor operations for restaurants wineries, movie theaters and family entertainment, zoos, museums and cardrooms bars. The state is one of the main SARS-CoV-2 foci in the United States (more than 300,000 cases, 7,000 deaths).

A study examining data for 355 Dutch municipalities finds evidence of a positive relationship between **air pollution** and Covid-19 cases, hospital admissions and deaths (Cole MA, Ozgen C, Strobl E (PDF); [The Guardian](#)).

[The Guardian](#): 30-year-old dies after attending 'Covid party' in Texas | 'I think I made a mistake, I thought this was a hoax, but it's not.' See also the [video](#) by Jane Appleby.

Do **men without a mask** look tough? ([The Guardian](#))

Returning **German tourists as superspreaders**? The CEO of the World Medical Association Frank Ulrich Montgomery proposes a two-week quarantine for holidaymakers returning from the Mallorca island ([audio in German](#)) after hundreds of drunken tourists celebrate in a pre-COVID atmosphere.

No re-opening of discos in France as the French Council of State estimates that the prolonged closing of the night clubs is not "disproportionate" ([Le Monde](#)).

Tuesday, 14 July

[Jackson et al.](#) publish a preliminary report about 45 healthy adults, 18 to 55 years of age, who received two vaccinations, 28 days apart, with **mRNA-1273** in a dose of 25 µg, 100 µg, or 250 µg. Read also the editorial by Editorial by Penny M. Heaton: [The Covid-19 Vaccine-Development Multiverse](#) and the audio interview [Covid-19 Vaccine Development](#), by Rubin, Baden and Morrissey.

Israel, Uzbekistan, Melbourne, California – certain states, areas and cities enter **new lockdowns**. [Le Monde](#) updates a non-exhaustive list of new pandemic hotspots, classified by number of inhabitants concerned and by country.

Jeneen Interlandi publishes [Why We're Losing the Battle With Covid-19](#). (The New York Times)

Michelle Goldberg publishes [In Some Countries, Normal Life Is Back. Not Here](#). (The New York Times)

Twitter comment on **British tourists in Spain**: "Parts of [Spain](#) in lockdown, the elderly shut away in care homes, we all wear masks in the street, but in Magaluf the antisocial and irresponsible Brits do whatever they please. It's shameful." ([The Guardian](#), text and video)

Wednesday, 15 July

If you read Spanish, read *Una sanitaria en L'Hospitalet de Llobregat: "El ambulatorio roza el colapso, peor que en abril"*. (El País).

Matthew J. Belanger, Michael A. Hill, Angeliki M. Angelidi, Maria Dalamaga, James R. Sowers, and Christos S. Mantzoros publish *Covid-19 and Disparities in Nutrition and Obesity*. (The New England Journal of Medicine)

Renee N. Salas, James M. Shultz, and Caren G. Solomon publish *The Climate Crisis and Covid-19 — A Major Threat to the Pandemic Response*. (The New England Journal of Medicine)

Thursday, 16 July

The French government decides that **wearing mask will be compulsory in closed public places** from next week. They describe the situation as “problematic” in *Mayenne*, “worrying” in *New Aquitaine*, and increasing number of cases in *Paris* and in *Finistère*. (Le Monde)

In Spain, 40% of recent outbreaks might have been associated with family events (“...a wedding in Tudela, a celebration of San Juan in a neighborhood of Castellón, a meal with friends in Alcanar (Tarragona).” (El País).

In a response to the paper by Jackson et al. (see 14 July), British researchers working on another Covid-19 vaccine at the University of Oxford **spread the word** that their vaccine, too, triggers two types of immune response: **the production of antibodies – proteins that can bind to the virus, preventing it from entering cells and flagging it to immune cells – but it also seems to result in the production of “killer” T cells – immune cells that attack infected human cells.** (The Guardian)

Danielle Renwick publishes *How quickly will there be a vaccine? And what if people refuse to get it?* (The Guardian)

Merlin Chowkwanyun and Adolph L. Reed publish *Racial Health Disparities and Covid-19 — Caution and Context*. (The New England Journal of Medicine)

If you read Spanish, read Miguel Ángel Criado: *Más de la mitad de los españoles ingresados por coronavirus han desarrollado problemas neurológicos* (El País)

Friday, 17 July

Israel returns to partial lockdown. All indoor gatherings of 10 or more people are banned. Restaurants return to takeaways and deliveries only. During the weekend, all shops, hairdressers and attractions are closed. All gyms and fitness studios are closed at all times.

Saturday, 18 July

Spain seems on the brink of a second COVID-19 wave. In the last 7 days, the country had 10 times more new cases than a month ago ([El País](#)). **Four million residents of Barcelona** and 12 municipalities around the city have been **urged to stay at home**. The regional Government announces that the restrictions also include the reduction of capacity in bars and restaurants and closure of nightlife venues, cultural activities and gyms, and a ban on gatherings of more than 10 people from Saturday.

In **France**, which already announced plans to make mask wearing mandatory in enclosed public spaces, authorities reported a sharp rise in the infection rate in Brittany. According to data released on Friday, the disease's reproduction rate in Brittany has risen from 0.92 to 2.62 between 10-14 July.

Infections in **India** pass one million.

Tom McCarthy publishes *'The virus doesn't care about excuses': US faces terrifying autumn as Covid-19 surges* ([The Guardian](#)).

Week 30

This week may be recalled as the timid beginning of the second European COVID-19 wave. At the beginning of the week, bars in Barcelona were ordered to limit the number of clients. On Saturday, Norway and the UK imposed a 10 (UK: 14) day quarantine on all people coming back from Spain, mostly holidaymakers, and Barcelona ordered the closure of discos, dance halls, etc. All over the continent, outbreaks are linked to seasonal farm laborers, family meetings and night life. 2020 tourism was severely affected by the continent-wide spring lockdowns. It is now doubtful that the holiday season will continue to summer's end.

The daily new cases in Australia:

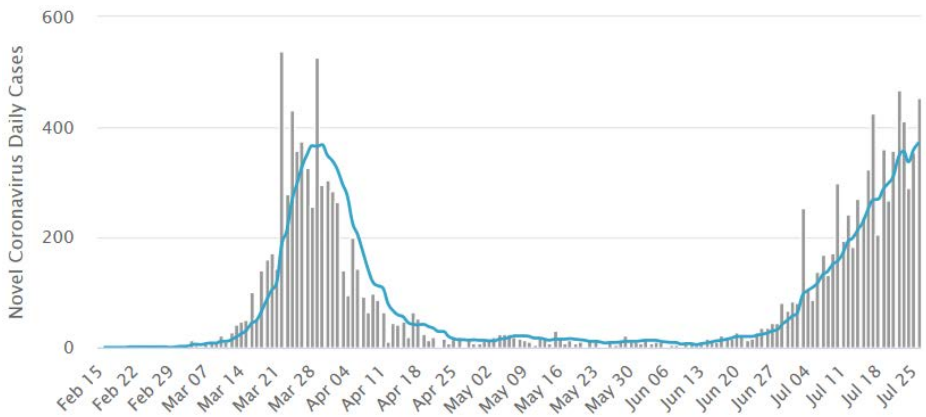


Figure 30.1. Daily new cases in Australia (blue line: 7-day monthly average).

Monday, 20 July

This is vaccine day. [Andrew Pollard and colleagues](#) report their phase 1/2 randomized trial of a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19); and [Wei Chen and colleagues](#) report results from a randomized phase 2 trial of an Ad5-vectored COVID-19 vaccine. Read also the comment by [Naor Bar-Zeev and William John Moss](#).

In Sao Paulo, 900 health professionals will participate in a phase 3 trial of a vaccine developed by the Chinese Sinovac Biotech laboratory. In total, the vaccine will be offered to 9,000 volunteers in six Brazilian states.

In France, the wearing of a mask becomes compulsory in closed places which are open to the public.

In Barcelona, the capacity in bars is limited to 50%. Visits to nursing homes are prohibited.

Tuesday, 21 July

Historic pact of the European Union to overcome the COVID-19 crisis: for the first time in its history, the EU member states will borrow money to finance an extraordinary economic stimulus with 390,000 million in grants and 360,000 million in credits, sending a strong message that they will continue to stay together. Presidents in the east and in the west will have taken notice (see also [The Guardian](#)).

Indian authorities claim that SARS-CoV-2 antibody testing of people living in the Delhi region showed that 23.5% had antibodies against the virus. Samples

from 21,387 people were examined. This percentage would be 50 times higher than the officially reported figures. Delhi, with a population of 29 million, has reported only 123,747 infections.

[Jennifer Steinhauer](#) and [Thomas Gibbons-Neff](#) explain how American military officials are trying to contain the spread of the SARS-Cov-2 in its ranks ([The New York Times](#)).

See also the feature by The Guardian: [How coronavirus is reshaping Europe's tourism hotspots](#). An opportunity to rethink their business model?

Barcelona reduces the capacity of its beaches ([El País](#)).

Wednesday, 22 July

Belgium is recording a significant increase in Covid-19 cases. During the period July 12-18, the number of new infections rose 89% with an average of 184 cases diagnosed per day, up from 98 the week before. Most cases are among people between 20 and 59 years old who were infected during parties or gatherings.

On the eve of a four-day long weekend in Japan, the governor of Tokyo calls on her constituents to stay at home, as the number of new daily cases of Covid-19 is sharply increasing in the region. As Covid-19 infections appear to be spreading widely, the Japanese capital is on its maximum alert level.

In Spain, 40% of people newly infected with SARS-CoV-2 are under 40 years of age and most do not know where they have been infected.

Thursday, 23 July

The Spanish newspaper [El País](#) sounds the alarm: The virus rebounds in Spain: data from 10 communities show more infections and more hospitalizations.

In the U.S., SARS-CoV2 testing laboratories struggle to find the chemicals and plastic pieces they need to carry out coronavirus tests ([The New York Times](#)).

[Lazaro Gamio](#), [Sarah Mervosh](#) and [Keith Collins](#) show *Where the Virus Is Sending People to Hospitals*.

Friday, 24 July

Authorities order the closure of nightlife (discos, dance halls, etc.) in Catalonia for at least 15 days. The hours of activity in casinos and game rooms are limited until midnight ([El País](#) + [El País](#)).

Norway reinstates mandatory 10-day quarantine for travelers coming back from Spain.

The U.K. makes wearing masks compulsory in stores.

The [New York Times](#) and [El País](#) ask “Who will receive the first COVID vaccines?”

Lauren Leatherby publishes [How the U.S. compares With the world’s worst coronavirus hot spots](#).

Saturday, 25 July

Catalonia exceeds 50 hospitalized daily, 10 times more than the figures reported by the Ministry of Health ([El País](#)).

In Belgium, wearing masks is now compulsory on markets, in shopping streets, in hotels, cafes and restaurants (except at the table).

With immediate effect, the [UK re-quarantines travelers from Spain](#). Those who come back home must isolate themselves for 14 days. This measure will [affect Spain’s tourism industry](#). But [not only Spain](#) is suffering.

If you read Spanish, read [El coronavirus ha repuntado en 30 provincias: el mapa con la situación de los contagios en cada una](#) | En el último mes han aumentado los casos y las hospitalizaciones en media España ([El País](#)).

Sunday, 26 July

A [tsunami of fake news](#) hurts Latin America’s effort to fight SARS-CoV-2. A report by [Tom Phillips](#) in São Paulo, [David Agren](#) in Mexico City, [Dan Collins](#) in Lima and [Uki Goñi](#) in Buenos Aires ([The Guardian](#)).

A surge in COVID-19 cases has forced a hospital in rural Texas to set up “death panels” to decide which patients it can save and which ones will be sent home to die. By [Michael Sainato](#).

[Victoria](#), Australia, reports a national record of 10 Covid-19 deaths.

North Korea reports the first COVID-19 case (...) and declares a state of emergency ([The Guardian](#)).

[How Hawaii avoided a coronavirus spike](#), but severely damaged its economy. [Lauren Aratani](#) explains.

If you read Spanish, read this: [Un verano con virus: qué hacer](#) | Viajar con amigos o ir a visitar a la familia unos días entraña riesgos. ¿Se comparte el salón? ¿Y el coche? ¿Se puede ligar? Los expertos explican cómo minimizar la exposición.

The true number of excess deaths due to COVID-19 is probably more than 50% higher than the officially reported data. See the analysis by [El País](#).

Monday, 27 July

If you understand German, meet [Dr Camilla Rothe](#) (6 minutes) who detected the first SARS-CoV-2 positive patient in Germany at the end of January. Within days, it became clear that asymptomatic transmission would play an important role in the pandemic. In the video interview, Dr Rothe looks back - and forward.

Notes

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